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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JULY, 1949

ORIGINAL ARTICLES

STUDIES OF THE EFFECTS OF FLAVONOIDS ON ROENTGEN IRRADIATION DISEASE

I. PROTECTIVE INFLUENCE OF RUTIN IN IRRADIATED DOGS*

By John B. Field, Ph.D., M.D.†

AND

Paul E. Rekers, M.D.

ROCHESTER, NEW YORK

(From the Department of Radiation Biology, University of Rochester School of Medicine and Dentistry)

Prior to the development of the atomic bomb, the effects of intensive ionizing irradiation on mammals were studied only occasionally.[16,26,36,37] The present report deals with some of the factors contributing to the mortality after roentgen irradiation, with particular emphasis on the significance of hemorrhage and sepsis. Attempts were made to reduce the predictable mortality of irradiated dogs and to check the hemorrhagic manifestations by administering flavonol glucosides.[29]

Methods. *Animals*: Young, healthy male or female hound or mongrel dogs of the beagle strain, approximately 1 year of age and of comparable sizes and weights, were used. They were maintained for a minimum of 4 weeks in quarantine prior to study. During this period they were rested, deloused, dewormed and vaccinated with anti-distemper vaccine. They were maintained for at least 1 week prior to irradiation in individual experimental kennels. They were given a diet consisting of 40:7 mixture of Friskies Dog Food Meal‡ and Evr Redy Meal§. All animals that developed anorexia in the post-radiated state were given fresh ground beef‖ and whole cow's milk, as well as the commercial foods.

Clinical observations were made daily and weights recorded semiweekly. Immediately after death, all organs were examined and sections were taken from all organs and obviously abnormal tissues. After fixation in Bouin's fluid, routine hemotoxylin and eosin stains of the sections were prepared for histopathological study.

* This paper is based on work performed under Contract No. W-7401-Eng-49 for the Atomic Energy Project at the University of Rochester. The authors gratefully acknowledge the counsel of Dr. H. Blair, director, and Dr. A. H. Dowdy, former director, Atomic Energy Commission, University of Rochester.

† Present address: Department of Medicine, The New York Hospital, and Cornell University Medical College, New York.

‡ Friskies Dog Food Meal, Albers Milling Company, Peoria, Ill. It consists of a minimum of 24% mixed proteins, 4.5% fat, 10% ash and a maximum fiber content of 4%.

§ Evr Redy Dried Meat with Bone, Rich Products Corporation, Rockford, Ill. It provides a minimum of 60% beef proteins and 5% fat, a maximum of 15% ash and 4% fiber.

‖ The consumption of all medication was facilitated by incorporating the drug in approximately 10-20 grams of fresh ground beef. Control dogs were also given an equal quantity of meat 3 times daily.

Irradiation Technique. The technique of single dose total body irradiation was used throughout. The dogs were exposed to the irradiations from a Picker industrial x-ray machine of 250 KVP, at a target skin distance of 37 inches. A 14.22 mm. parabolic aluminum and an 0.53 mm. copper filter were used; the half-value layer was 2.15 mm. of copper. The dosage usually delivered to the dorsum of the skin of dogs was 350 r. This value was determined each time from direct measurement in air with a Victoreen ionization chamber at a trial run. The dogs were enclosed separately in individual small wooden boxes fitted with loose open screen tops which permitted movement during irradiation.

Hematology. Accepted methods were used in the examination of the peripheral blood.[28] All blood samplings were done by jugular venipuncture without stasis at a standard time of the morning, both pre- and post-radiation, when the animal was in a fasting state. The following elements were measured: Erythrocytes, hemoglobin, white blood cells, volume of packed cells and sedimentation rate. The relative and absolute proportions of neutrophils, eosinophils, basophils, lymphocytes, monocytes, myelocytes, blast and unusual forms were measured in smears of peripheral blood. Erythroblasts and reticulocytes were counted, and an evaluation of anisocytosis, poikilocytosis and basophilic stippling was also noted. The platelets were counted after treatment with a brilliant cresyl blue diluting fluid.

Experimental. *Biologic response to irradiation.* The reactions of animals to whole body irradiation have been described previously,[2,8,13,16,26,27] critical and determining factors being species and dose. In the present study the dogs given a penetrating single dose of 350 r at the target skin distance exhibited no gross external changes for several days, although a leukopenia was detectable within 1-to-2 days. An increase in body temperature was not always detected at this time. Both a thrombocytopenia and an anemia appeared after 4 days, at which time the food consumption of the dogs also began to decrease. Further signs of gastro-intestinal irritability, infrequent vomiting and some diarrhea appeared somewhat later. Anorexia became profound from the 7th to the 21st day when oropharyngeal ulceration and gingivitis also very frequently appeared. The body weight remained stable during the first week; weight loss was observed in the 2nd and 3rd weeks, after which normal growth was resumed. Hemorrhagic tendencies, observable most frequently as oozing in the gingival margins or petechiae in the unpigmented epidermis of the dog, made their first external appearance about the 10th day. The early appearance of bloody stools, epistaxis or hematemesis in an otherwise healthy appearing dog proved to be of serious prognostic significance, as were a marked lassitude, an unkempt appearance and anorexia to fluids as well as to diet. Twenty two of 37 control dogs (60%) died within 13 to 30 days (average 20 days) after irradiation.

A gross examination of the animals which succumbed always revealed a hypoplasia of the marrow, spleen and lymph nodes associated in general with a panhematopenia. Most frequently associated conditions were petechiae, ulcerations and bleeding into the various portions of the intestinal tract, pulmonary hemorrhages and occasionally indications of a generalized sepsis. Histopathological examination did not indicate overwhelming infection of critical organs such as the lungs, hematopoietic centers and abdominal viscera, and there was no evidence of peritonitis or pleuritis.

Effect of lemon peel infusion in irradiated dogs. An aqueous concentrated extract of lemon peel¶ similar to Szent-Gyorgyi's original preparation[30,33] in the form of enteric-coated 200 mg. tablets was given to 11 dogs orally 3 times daily beginning 1 week prior to irradiation and continued until 28 days post-radiation. Four of these

¶ Mr. A. J. Lorenz, Director of the laboratories, and Mr. W. E. Baier, Manager, California Fruit Growers' Exchange, Ontario, California, supplied the lemon peel preparation.

dogs died with typical signs of irradiation toxicity. Only transitory symptoms of intoxication appeared in 2 of the surviving dogs. A routine hematological examination of the entire group of 11 did not indicate any significant difference between it and the control group of 37 dogs not receiving any dietary supplement. Nevertheless, the lemon extract proved effective in increasing the survival of irradiated dogs: 36% (4 of 11) of the supplemented dogs succumbed at an average of 21 days (range, 11 to 31 days) after irradiation compared to the 60% (22 of 37) mortality observed in 20 days in the control dogs.

Effect of ascorbic acid in irradiated dogs. The value of citrus concentrates in alleviating experimental and clinical purpura has been ascribed[22,38] to the vitamin C present. Unlike man, the dog ordinarily synthesizes adequate quantities of this vitamin. Furthermore, the vitamin C analysis of the lemon peel preparation was only 1.8 mg. per 200 mg. tablet. It would thus appear that this quantity, insignificant in relation to the dog's dietary consumption, would play no role in the protective effect of the lemon concentrate against irradiation. This was demonstrated in an experiment in which 12 dogs were given 100 mg. of l-ascorbic acid orally 3 times daily beginning 1 week prior to irradiation. Six dogs (50%) succumbed after 12 to 14 days post-radiation, and at autopsy exhibited a typical widespread hemorrhagic diathesis. The clinical course and hematological data of all animals were identical to the control irradiated dogs.

Effect of rutin in dogs irradiated with 350 r—rutin given both before and after irradiation. Certain flavonol glucosides have been reported to be effective in suppressing purpuras of unknown etiology in the guinea pig and man,[14,31] and the active principle has been designated by Szent-Gyorgyi, "vitamin P." Extracts of lemon peel are rich in "vitamin P" activity. Accordingly rutin,# a rhamnoside typical of this type of compound, was tested for its effectiveness against the irradiation syndrome in dogs. Marked differences in mortality and morbidity were dependent upon the chronological relationship of onset of rutin treatment to irradiation. First recorded are the observations when rutin administration *preceded* the irradiation and was continued thereafter.

1. *Mortality and incidence of hemorrhage.* Rutin was given orally in 50 mg. gelatin capsules to a group of 27 dogs 3 times daily beginning 1 week prior to irradiation and continued until 28 days post-radiation. The data were obtained in 5 separate trials performed at different times during the year. Control studies were carried out simultaneously. In each trial the results were identical and a summary of the mortality, survival times and clinical evidence of hemorrhage compared to similar data from the control dogs is given in Table 1. The weight curves of the rutin-treated animals, in general, paralleled the weight curves of the control group of animals.

2. *Petechiae formation.* By applying a circular suction cup of 1.8 cm. in diameter at a standard negative pressure of approximately 60 mm. Hg. to the clear unpigmented epithelium of the dog's abdomen for 2 minutes, an attempt was made to study induced petechial formation. This type of procedure provided a crude evaluation of post-radiation hemorrhagic tendencies. In brief, it can be stated that the rutin-treated dogs exhibited fewer and small-

Obtained in generous quantities from the Eastern Regional Research Laboratory, U. S. Department of Agriculture, Philadelphia, Pennsylvania, through the courtesy of Dr. J. F. Couch and also the Abbott Laboratories, North Chicago, Illinois.

er induced petechiae than the untreated dogs.

3. *Coagulation time.* Neither the prothrombin nor fibrinogen appeared to be depleted in irradiated dogs, although there was a minor prolongation of the whole blood clotting time.[2] The drawn venous blood from dogs was placed into tubes and the coagulation time determined.[20] The clotting time before irradiation varied in individuals from 6 to 12 minutes (mean 9) and in the terminal state from 6 to 50 minutes (mean 18). There was a crude

TABLE 1.—THE INFLUENCE OF RUTIN ON IRRADIATED DOGS (350 r)

	Number of Dogs		Mortality	Survival (a) Post-Radiation		Exhibiting Gross Bleeding (b)	Showing Petechiae
	at start	survived	per cent	average days	range days	per cent	per cent
Control	37	15	60	20	13-30	64	84
Rutin-Treated							
Group 1(c)	27	24	11	21	16-31	22	22
Group 2(d)	6	4	33	16	14-18	66	50
Group 3(e)	5	1	80	16	13-20	40	100
Group 4(f)	5	2	60	18	11-28	40	80

a. Calculated from the animals which succumbed.

b. Bleeding from the gingival surfaces, or any of the orifices, nasal, oral or vaginal or hematoma formation.

c. Group 1. 50 mg. rutin, 3 times daily, was given for 7 days before as well as after irradiation.

d. Group 2. 50 mg. rutin, 3 times daily, was given for *only* 7 days before irradiation.

e. Group 3. 150 mg. rutin, 3 times daily, was given beginning the second day *after* irradiation.

f. Group 4. 400 mg. rutin, 3 times daily, was given beginning the day *after* irradiation.

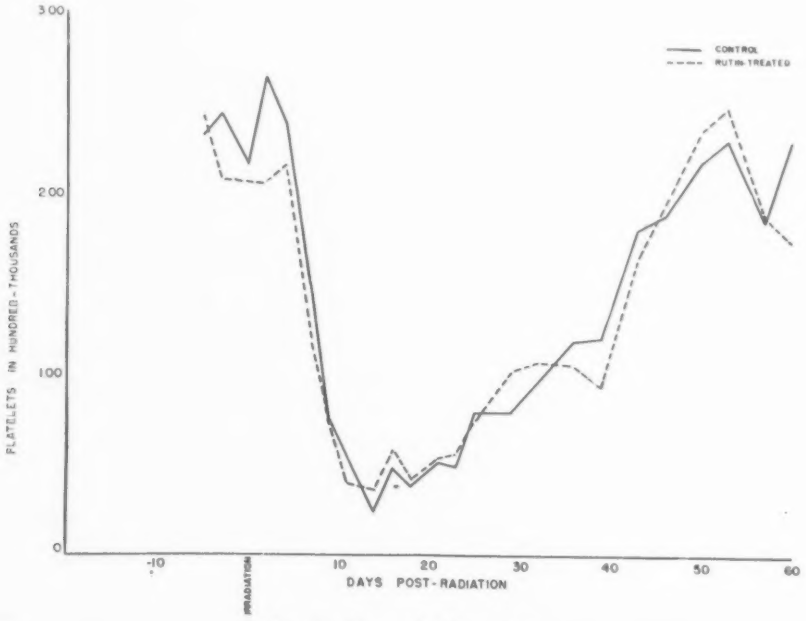

Fig. 1.—Mean platelet values.

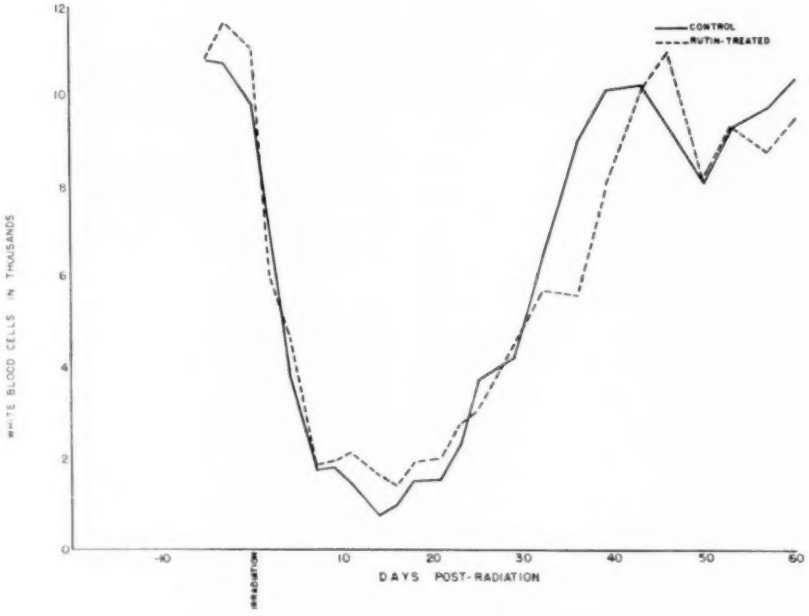

Fig. 2.—Mean white blood cell values.

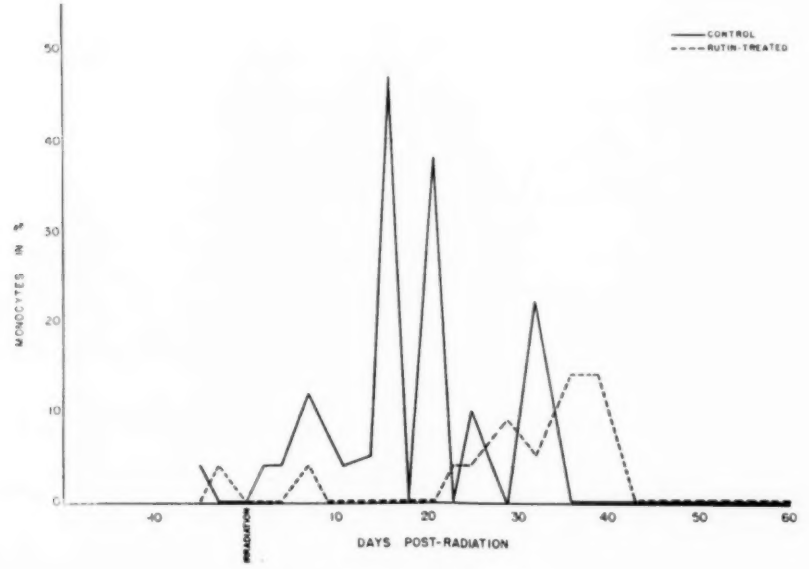

Fig. 3.—Mean monocyte values.

relationship of coagulation time to the hemorrhagic tendency, but at least one animal succumbed to a "hemorrhagic death" with the coagulation time identical with that obtained pre-radiation. The coagulation time of dogs receiving rutin was similar to that of control dogs.

4. *Hematological changes.* The characteristic changes in the peripheral

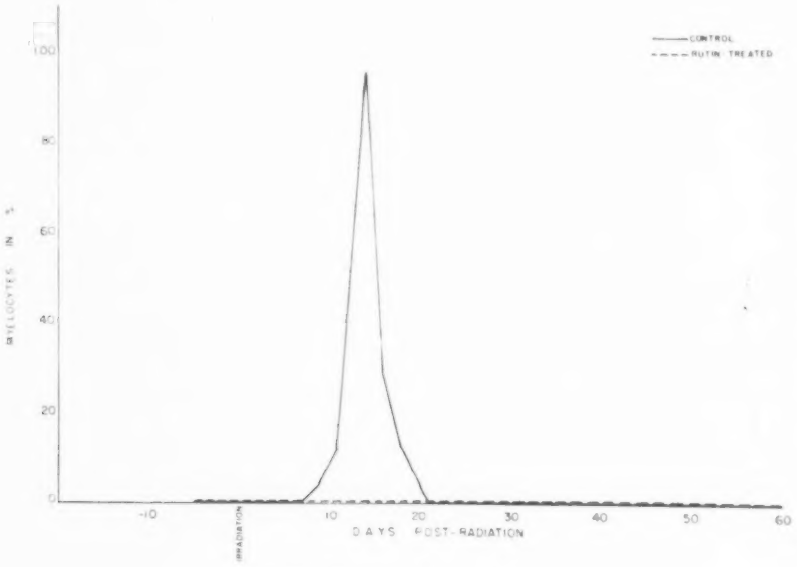

FIG. 4.—Mean myelocyte values.

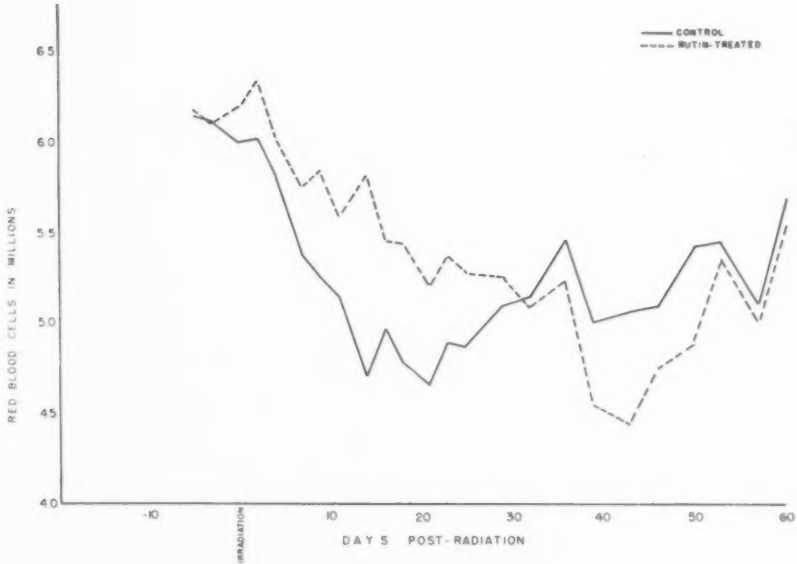

Fig. 5.—Mean red blood cell values.

blood of dogs exposed to 350 r are given in Figures 1-10, and the findings from dogs treated with rutin are given in the same figures. Each curve represents the means obtained either from the total or surviving dogs in each group.

To summarize the hematological results: a. The thrombocytopenia (Fig. 1) and leukopenia (Fig. 2) of both control and rutin-treated dogs were identical.

b. Similarily, the comparative curves of the total neutrophil and lymphocyte elements exhibited no significant differences. Also there were no significant differences in the quantity of eosinophils or basophils.

c. The comparative estimation of monocytic and myelocytic elements is given in Figs. 3 and 4. The myelocytes of the control dogs were increased from the normal of zero to almost 1% between the 8th and 20th days post-radiation. Also, the leukoblast forms and monocytic cells of the control dogs were significantly increased about this time.

d. The erythrocyte count and corresponding hemoglobin of the rutin-treated dogs declined significantly less rapidly than the control irradiated dogs until approximately the 33rd day post-radiation (Fig. 5). After this day the tendency towards restoration of normal levels was somewhat greater in the untreated dogs.

e. The erythroblasts in the blood of the rutin-treated dogs (Fig. 6) were significantly more numerous than those in the blood of the control dogs from about the 21st to the 43rd post-radiation days. A corresponding increase in the nucleated red blood cells also was seen in the rutin-treated animals from about the 21st to the 47th post-radiation days (Fig. 7).

f. An increase in the basophilic stippling of the red blood cells of the untreated dogs was observed between the 21st and 47th days. The reticulocytes of both rutin-treated and control dogs were similar until between the 39th and 60th days when the count in the surviving control dogs was significantly increased (Fig. 8).

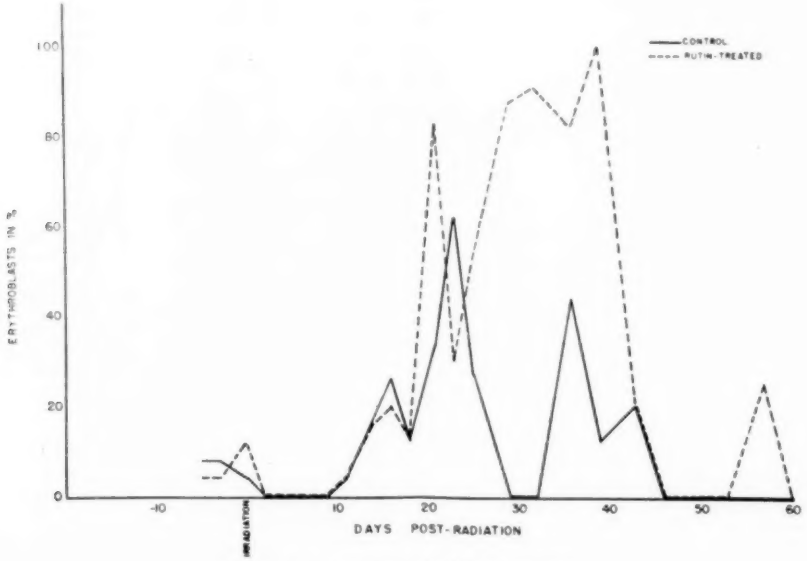

Fig. 6.—Mean erythroblast values.

g. Although there was no great difference in degree of anisocytosis of the red cell elements, it would appear that there was some increase in the degree of poikilocytosis in the control dogs (Fig. 9) during most of the post-radiation period.

h. The corrected sedimentation rate of the red cells is given in Fig. 10. Although the sedimentation rate of both

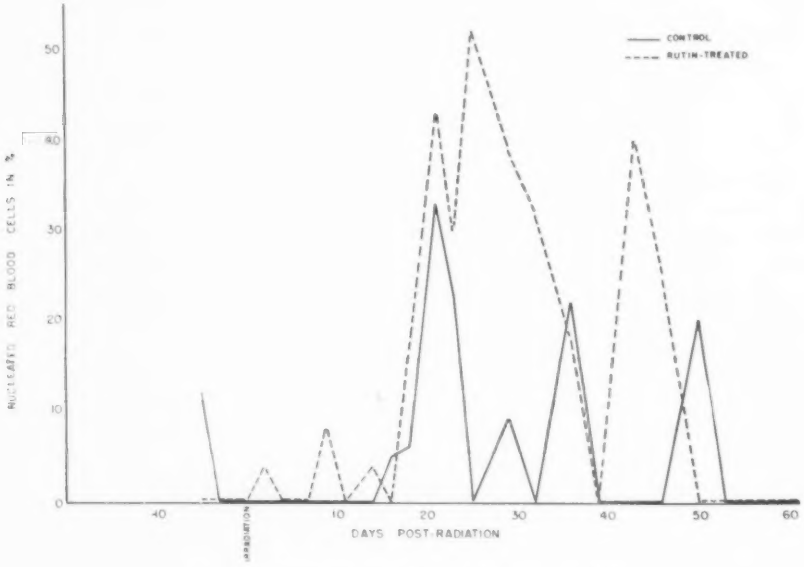

Fig. 7.—Mean nucleated red blood cell values.

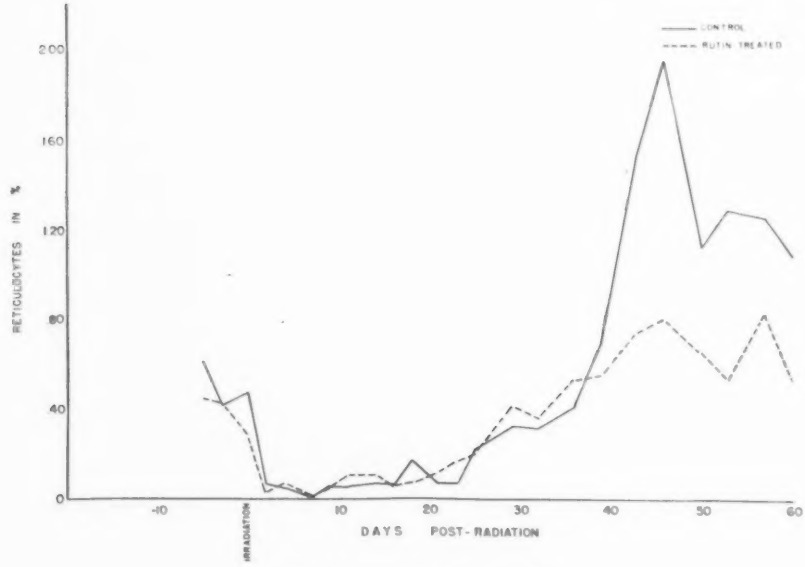

Fig. 8.—Mean reticulocyte values.

rutin-treated and control dogs was shown to increase rapidly in the post-radiated state, the increase of the control dogs was the greater.

5. *Post-mortem examination.* All animals which succumbed from the effects of irradiation were grossly similar and it was impossible to distinguish the 3 rutin-treated dogs that died from the 22 untreated dogs. Common

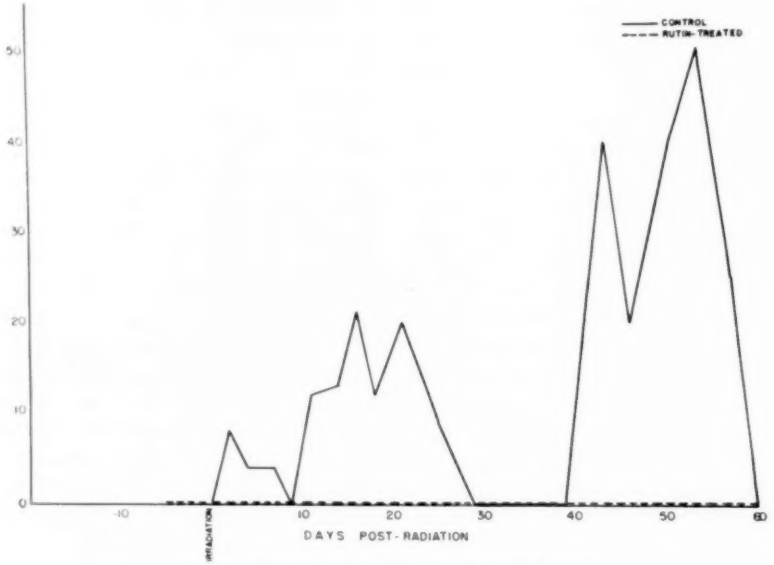

Fig. 9.—Subjective evaluation of poikilocytosis.

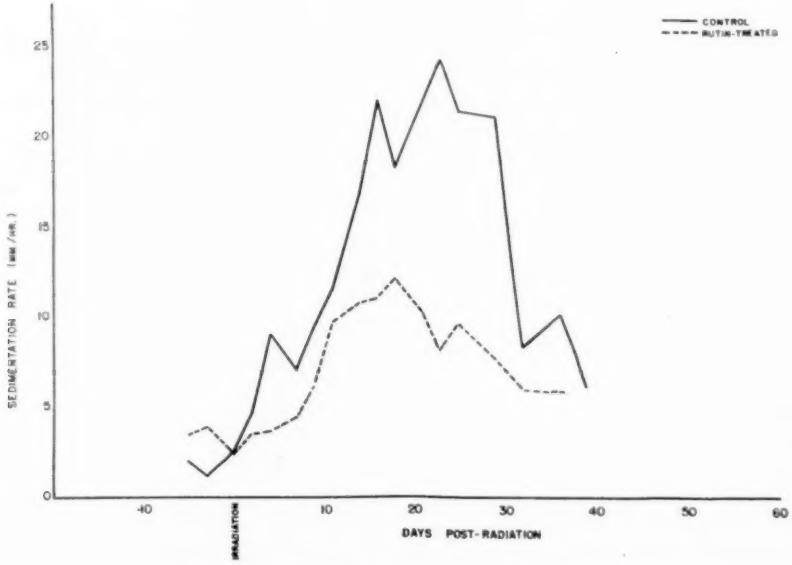

Fig. 10.—Mean sedimentation rates.

findings were hypoplasia of the bone marrow, lymph nodes and spleen, generalized purpura and petechiae formation, intrapulmonary, gastric or intestinal hemorrhage and occasional signs of alveolar and pulmonary sepsis.

Likewise, autopsy examination of all animals in the state of clinical recovery, 35 to 60 days post-radiation, revealed only the anticipated indications of recovery from irradiation toxicity with marrow hyperplasia, hyperemia of the gastric and intestinal mucosa and occasional indication of a previous purpuric state. The spleen and lymph nodes showed considerable variation. The predominating picture was that of hypoplasia or early regeneration.

A careful study of histological sections from the organs of all animals contributed little to the findings of gross organ examination and previous studies[2,8,13,16,26,36,37]. It was impossible to differentiate in any way between the rutin-treated and untreated dogs. Using the usual tissue strains, the morphological state of the vascular systems of both groups appeared identical.

Effect of rutin in dogs irradiated with 350 r — rutin given pre-radiation only. Rutin was fed as 50 mg. capsules 3 times daily to 6 dogs beginning 1 week before irradiation. Two of the 6 (33%) died (Table 1). The hemorrhagic tendency and irradiation illness were more severe than seen in the dogs given rutin both before and after irradiation (mortality 11%) but less than that seen in untreated control dogs (mortality 60%).

Effect of rutin in dogs irradiated with 350 r—rutin given post-radiation only. In one test rutin was fed as 150 mg. capsules 3 times daily to 5 dogs beginning the second day after irradiation with 350 r. Four of these 5 dogs (80%) died. In a second test 400 mg. were administered 3 times daily to 5 dogs beginning the day after irradiation. Three of these 5 dogs (60%) died. In the control series 22 of 37 dogs died with a mortality of 60%. A summary of the mortality and hemorrhagic tendencies is given in Table 1. In general, this treatment appeared to have no significant effect on the effect of irradiation disease from examination of the clinical course, the peripheral blood or from post-mortem observations.

Effect of rutin in dogs irradiated with 450 r — rutin given both before and after irradiation. The degenerative reaction of dogs to 450 r single dose irradiation was, as to be expected from the data on 350 r irradiation, more acute and lethal. However, in the experience of this laboratory it has been difficult to utilize so large (or larger) an acute dose to attain 100% mortality; that is, an occasional dog survives. Thus, 4 of 5 control dogs given 450 r (80%) died within 14 to 29 days (average 18 days). When 50 mg. of rutin were given orally 3 times daily beginning 1 week prior to irradiation to 4 dogs, 3 (75%) succumbed within 15 to 17 days (average 16 days).

Studies on the excretion of rutin in urine. The amount of rutin excreted by dogs receiving 100 mg. daily was determined by the method of Couch.[6] *In vitro* recovery tests on fresh urine and on urine stored for 72 hours indicated an average recovery of the drug of 99%. Only small amounts of rutin were recovered after the 3rd day of administration, and with supplements of 2.8 and 5 gm., usually only small increments in the output were noted (Table 2). Total body irradiation did not appear to affect the urinary excretion of the drug.

Bacteriological studies. The flavonols and rutin have some degree of antibiotic activity.[3,24] The development of signs of sepsis in the irradiated dogs and the undisputed contribution of uncombated infection in the absence of adequate leukocytic response to the

TABLE 2.—URINARY EXCRETION OF RUTIN WHEN 100 MG. WAS FED 3 TIMES DAILY

	Dog 1 Days after start of feeding	Rutin in Urine mg./24 hours		Dog 2 Days after start of feeding	Rutin in Urine mg./24 hours
Pre-radiation	1-2	0.0	Pre-radiation	1-2	0.0
	3-5	0.5		3-5	0.8
	6••	0.3		6-9	2.4
	7••	2.1		10•	1.8
	8	8.0		11-14	5.8
	9	2.7		15••	3.3
Post-radiation†	11-21	2.0		16••	5.7
	22••	1.7		17•	2.8
	23••	7.8		18	7.0
	24	3.9		19	4.1
	25	6.2		20	26.6
	29	0.0	Post-radiation†	21-25	2.6
	32	1.8		29	0.0
	35-50	0.3		31	1.8
				35-39	0.0
				42	5.3
				45-50	0.1

• Supplementary feeding of 5 gm. rutin.
•• Supplementary feeding of 1.4 gm. rutin.
† 350 r single dose total body irradiation.

irradiation syndrome made a bacteriological survey imperative.

Under aseptic conditions, routine blood samples were withdrawn from all irradiated dogs at frequent intervals and in the terminal state. Post-mortem samples were taken aseptically from the heart. The blood was cultured in a variety of nutrient media under both aerobic and anerobic conditions.

No detectable differences were observed in the frequency or type of septicemia between the flavonol-treated dogs and the untreated dogs. For this reason, the data from all blood cultures to date were pooled (Table 3). The organisms isolated and their frequency were: Clostridium welchii (16 times), hemolytic streptococcus (7), anerobic gram-positive rod forms (5), B. coli (4), Staph. albus (3.) and unidentified gram-negative rod forms (3); obtained twice each were B. subtilis and Clostridium fallax; and obtained once each were Staph. aureus, B. pyocyaneus, an unidentified staphylococcus, an unidentified diphtheroid form, an unidentified hemophilus organism and a gram-positive aerobic rod.

TABLE 3.—A SURVEY OF BLOOD CULTURES TAKEN FROM IRRADIATED DOGS

	Positive	Total	% Positive
Pre-radiation	0	25	0
Post-radiation	7	114	6.1
0- 7 days	5	70	7.1•
8-30 days	25	280	8.9
	7	86	8.1•
48 hours pre-mortem	13	28	46.4
24 hours pre-mortem	13	21	61.9••

• Data from dogs eventually succumbing to irradiation toxicity abstracted from the total number.

•• These data confirm the observations of Warren and Whipple[37] which demonstrated that direct x-irradiation to the abdomen produces destruction of the intestinal epithelium, but a bacterial invasion of tissues, lymph or blood by bacteria does not occur until the agonal state. This situation, as they point out, is quite common to other conditions.

Effect of whole body irradiation on the fragility of the red blood cells. The rate at which anemia developed in the dogs continuously treated with rutin [illegible] significantly less than in the cont[illegible] dogs following whole body expo[illegible] to 350 r irradiation (Fig. 5). A s[illegible]estion was entertained that the red cell membrane is weakened in

irradiated dogs, producing some disintegration *in vivo*.[19] This was investigated by examining the resistance of erythrocytes from irradiated dogs to induced hemolysis. In the procedure adopted duplicate determinations were made with saline solutions differing from tube to tube by 0.02%, and the end point of hemolysis was determined with a photoelectric colorimeter.[17] Serial determinations of blood samples withdrawn from a variety of normal non-radiated and irradiated dogs, many in the terminal state with profound purpuric manifestations, consistently provided cell lysis beginning at 0.40 and completed at about 0.30% saline solution with no differences between irradiated and non-radiated dogs.

Discussion. An appreciation of the action of flavonols in the irradiated dog provokes an acknowledgment of the uncertainty surrounding the irradiation disease. As yet, there is no agreement as to the individual significance of sepsis, hemorrhage or the nondescript toxic action of irradiation products in the terminal course.[26,27,29,36,37] In certain irradiated animals there is little question of the terminal role of hemorrhage into vital organs.[2,7,8,21,26,27,34,35] In others where this was less obvious, it has been convenient to attribute the exitus to the effects of sepsis.[34] Finally, there are those animals who succumb before either hemorrhage or sepsis could be expected and these do not exhibit any obvious understandable cause of death.

The significant reduction in the hemorrhagic diathesis seen in the 350 r irradiated dogs treated pre- and post-radiation with rutin suggests that through reducing the hemorrhagic tendency the glucoside exerts its sparing action on the predictable rate of mortality. The failure of rutin to spare dogs treated *after* irradiation requires some consideration. Data from this report suggest that the dog is relatively unsaturated in regard to the flavonol as measured by a lapse of several days before rutin can be detected in the urine. Apparently, during the pre-radiation period the dog is able to saturate itself, and presumably this provides for maintenance or repair of an altered vascular system. This would explain the partial effectiveness of giving rutin even in relatively small doses of 50 mg. 3 times daily for 1 week up to the time of irradiation, but not after. In the face of decreased alimentary absorption following irradiation[4,23] it is probable that the rutin available after oral administration would be limited, and thus it cannot exert its maximum therapeutic effect. The failure of rutin to alter the increased lethal effects of 450 r irradiation in dogs is at the moment a matter of conjecture. It appears, however, that rutin controls the hemorrhagic tendency which is a predominant factor in mortality in mid-lethal irradiation (350 r). At higher doses hemorrhage appears to be less responsible than a generalized intoxication for death. It is this non-specific reaction which is the primary cause of mortality in acutely irradiated rats, mice and guinea pigs in which rutin offers little or no protection.[12]

Since the flavonol glucosides have been shown to have antibiotic activity,[3,24] it is necessary to consider the role the drug would play in combating the sepsis which follows irradiation. Terminal septicemia following irradiation was exhibited in no more than 62% of dogs so studied, and it appears unlikely that rutin antibiosis would significantly benefit the survival rate.

Allen and Jacobson[1,2] have recently reported that the level of heparin or a heparin-like agent in the blood of irradiated dogs was increased, and to this was attributed the hemorrhagic manifestations. The injection of such antiheparin agents as toluidine blue and protamine temporarily restored the

prolonged coagulation time to normal and halted the purpuric manifestations. Rutin, *per se*, did not reduce the hypocoagulability of blood from irradiated dogs. In a subsequent report the relationship of rutin and heparin will be discussed but there is no evidence to indicate that rutin can restore the prolonged coagulation time produced with heparin. Uniformly, however, all dogs had a reduction of the peripheral platelet count which was correlated with obvious depression of marrow activity. It has been observed that heparin, *per se*, can induce a thrombocytopenia,[10] and this presumably results secondarily to a visceral clumping of platelets.[5] However, the intimate time relationship of thrombocytopenia with onset of hemorrhagic syndrome has impelled the natural conclusion that the two were inseparable.[8,32] In the present observations in irradiated dogs, severe prolonged thrombocytopenia could be dissociated from the purpuric manifestation by the administration of rutin.

An interpretation of the hematological differences uncovered between irradiated dogs with and without pre- and post-radiation rutin therapy invites considerable speculation. In summary, there was found (a) a more rapid decline of the erythrocyte count in the untreated dogs, (b) a significant elevation in erythroblasts and nucleated red blood cells between the 20th and 45th post-radiation days in the rutin-treated dogs, and (c) an increased reticulocyte response between the 30th and 60th post-radiation days and an increased basophilia of the erythrocytes between the 20th and 50th post-radiation days in the untreated dogs.

Assuming that vascular dysfunction permits increased diapedesis to occur during the early post-radiation period before arrest of erythrocyte maturation in the bone marrow would significantly reduce the peripheral concentration of red cells, it appears plausible that prevention by rutin of increased diapedesis would serve to maintain the total blood count. This is the more likely explanation in the absence of a positive effect of the flavonol glucoside on the irradiated marrow or positive indication that erythrocyte fragility is increased in the irradiated dog.

An increased reticulocyte response usually characterizes augmented erythropoiesis. The greater reticulocyte response of the 15 surviving untreated dogs was matched against the average reticulocyte count of 24 surviving rutin-treated dogs. The dogs receiving rutin did not suffer the low ebb of anemia to which the untreated dogs fell, and therefore the recovery stimulus to the untreated dogs was conceivably the greater. This idea was supported by directly comparing the reticulocyte counts of several rutin-treated dogs who had as severe an induced post-radiation anemia as the untreated dogs. Here the recovery curves of both erythrocytes and reticulocytes were very similar.

We have not observed rutin to alter an induced change in capillary permeability in animals. In the absence of a more realistic explanation for this and an invariable increased spontaneous petechiae formation and other signs of purpura following irradiation, it is proposed that the irradiation syndrome stems from a localized reduction in the structural strength or a dysfunction of the vascular system, permitting disruption and uncontrollable diapedesis. It would appear that the prevention of otherwise fatal exsanguination or embarrassment by hemorrhage of vital organs through this route might provide a life-saving support until the ordinary synthetic capacity of the organism can recover from the inhibitory effects of roentgen irradiation. In this regard, it is pertinent to mention that at least 6 dogs given the

flavonol therapy have been observed to survive with minimum hemorrhagic signs in the presence of prolonged (10 to 18 days) drastic leukopenia and thrombocytopenia. In distinct contrast, recovery of untreated dogs with persistent, severe depression of the same blood elements has rarely been observed in this laboratory. To what extent "vitamin P" substances protect against the anaphylactic and histamine factors reported to occur following ionizing irradiation[2,9,23] remains to be clarified.[12]

It is imperative to offer some clarification in the confusion presented by the use of the terms capillary "permeability" and "fragility" in the accumulating literature on "vitamin P". In no test reported here have we given data which would substantially support a claim that rutin *per se* affects the specific membrane permeability phenomenon. In experiments still in progress such confirmative and specific observations have yet to be made. However, it is felt that in some manner, as yet not elucidated, the rhamnose glucoside aids in the control of vascular dysfunction of dogs given 350 r whole body x-irradiation when the substance is given both pre- and post-radiation. Prevention of vascular damage reduces the hemorrhagic extravasation. The extent to which this is limited to the capillaries is a topic for further investigation.

The failure of vitamin C to affect the course of irradiation toxicity, which has also been reported elsewhere,[1] is in contrast to the significant protection given by rutin. With these findings, support is given to the long contested claim by Szent-Gyorgyi and his collaborators[30,33] that a factor, such as "vitamin P", does exist. It is unfortunate that recent efforts in this field deal only with isolated pharmacological characteristics and indirect types of biological assay of the family of flavonoids to which some "vitamin P" activity is attributed.[15,25] In the main, other investigations have utilized the epinephrin-sparing action of the "active" agents. The work presented here presumably involves an alteration in vascular function with "vitamin P" substances reducing the rate and manner of this dysfunction. Thus, the roentgen irradiation type of dog assay presents itself as an objective method of direct biological test for "vitamin P" potency. With this method it has already been possible to demonstrate that, with reference to rutin, considerable variation exists in closely related compounds.[11]

Summary. 1. In dogs given 350 r single dose total body x-irradiation, 60% (22 of 37) untreated animals died, whereas when a preparation from lemon peel was administered continuously pre- and post-radiation, 36% (4 of 11) of the animals succumbed. When the flavonol glucoside, rutin, was administered continuously pre- and post-radiation, 11% (3 of 27) of the animals succumbed; when given pre-radiation only, 33% (2 of 6) dogs succumbed; when given post-radiation only, 80% (4 of 5) and 60% (3 of 5) dogs succumbed.

2. Clinical signs and post-mortem evidence of a hemorrhagic diathesis were most prominent in the untreated dogs and the dogs given rutin post-radiation only. A generalized purpura was observed in the dogs tested with lemon peel extract or rutin, but petechiae and spontaneous purpura were less frequent in dogs given rutin before and after the irradiation than in dogs not receiving rutin. The reduction in hemorrhagic signs existed despite a depression of the blood platelets. Moderate hypocoagulability existed in both control and rutin-treated dogs.

3. Hematological studies indicated that the rate of anemia production and the magnitude of the increased sedimentation rate were reduced while the

erythroblast forms and nucleated red blood cells were increased in the rutin-treated animals. Irradiation of dogs with 350 r did not increase the fragility of erythrocytes.

4. Septicemia was demonstrable in no more than 62% of the dogs terminally. Thus, it is suggested that a primary cause of death in the 350 r single dose total body x-irradiated dogs is a bleeding tendency which may be associated with a vascular dysfunction as well as a thrombocytopenia.

5. The existence of an entity such as "vitamin P" affecting vascular fragility is supported by the present report. The technique of roentgen irradiation to induce a bleeding tendency in dogs may prove useful in an assay for "vitamin P" potency.

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EVIDENCE ON THE GENESIS OF CERTAIN COMMON NASAL DISORDERS*

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Proetz[28] and Polson[26] among others have presented evidence which indicates that swelling of the turbinates, obstruction and hypersecretion in the nose, from whatever cause, may predispose the individual to "common cold", as well as to more chronic, recurrent disorders of the nasal and paranasal spaces including sinusitis.

Dochez and his associates[5] have adduced strong evidence to indicate that this process of nasal hyperfunction is often initiated by a filterable virus with the ultimate production of a typical "common cold". On the other hand, the work of other observers[1,2,15] has indicated that viruses are not responsible for all such reactions of nasal hyperfunction. Other stimuli and situations which have been observed to provoke vascular engorgement, swelling, hypersecretion and obstruction in the nose are: inhalation of irritant dusts and chemical fumes[16,24], bright lights[28], chilling of the body surface[10,22,29], inhalation of pollens and the other substances to which the subject is "sensitive"[11,34], menstruation and pregnancy[20,21], sexual excitement[17,25,32], and life experiences which engender insecurity and conflict[4,27,33].

In an attempt to illuminate further the role of nasal hyperfunction in the natural history of chronic nasal disorders, man and his nose were investigated as a unit. Cognizance was taken not only of changes observed in nasal function, but also of the life setting in which these alterations in nasal function occurred, attention being focused on the emotional reactions, attitudes and behavior of the individual. Some of the observations and conclusions evolving from this method of clinical investigation are detailed in this communication. Some have been presented elsewhere[15,36] and a more detailed and comprehensive report has been assembled as a monograph[12].

Method. Observations were made from 1 to 7 times weekly and for periods lasting from 1 to 8 months on 112 subjects, varying in age from 13 to 60 years. They were examined under uniform conditions at approximately the same time each day.

Examination of Nasal Structures. A warmed nasal speculum illuminated by reflected light

* Supported in part by grants from the Commonwealth Fund and the estate of Lester N. Hofheimer.

from a daylight bulb was used for examination of the nasal structures. The degree of engorgement and swelling of the turbinates, the amount of secretion and the degree of nasal obstruction were estimated in terms of 0 to 4 plus in accordance with well defined standards[13]. Measurements of blood flow were made by comparing the color of the nasal mucous membrane with a suitably calibrated color chart[23]. The colors, quantitated by the method of Munsell, ranged from a pale yellow-red to a deep cardinal, and were expressed as numbers from 0 to 100. It has been shown elsewhere that color changes in mucous membranes reflect variations in blood flow[30]. In addition to these changes, the following were also carefully noted: (1) awareness of accumulated secretion in the nasal cavities: (2) sneezing; (3) burning or tickling sensations; (4) post-nasal drip; (5) pain. The latter was roughly quantitated in terms of 0 to 10 plus, 10 plus representing pain of the highest intensity in the subject's experience.

Elsewhere[13,14,36] it has been demonstrated that the inhalation of noxious chemical fumes or allergens elicits a prompt and appropriate pattern of defense at the head end of the organism, consisting of hyperemia of the nasal mucous membranes, swelling of the turbinates, hypersecretion, and obstruction to breathing. This appeared to represent an attempt to shut out, neutralize, and wash away the noxious agent. A similar pattern of nasal hyperfunction occurred following other threats to bodily integrity which included: (1) experimentally induced pain; (2) cutaneous chilling; (3) exposure to cold atmosphere; and (4) discussion of pertinent emotional conflicts attended by feelings of humiliation, frustration, resentment and guilt engendered by a life situation which had special significance because of the individual's past conditioning experiences. Thus it appeared that the defensive pattern of shutting out, neutralizing and washing away in the nose can be called into play by the organism when its integrity is endangered by a wide variety of direct and symbolic threats and assaults. In some instances, the hyperfunction was well tolerated, but in others it was associated with nasal symptoms.

The following protocols are representative of more than 4,000 observations on 112 patients carried out in an attempt to determine the relevance of changes in the nose which accompany emotional stress, to tissue damage and nasal disease, and to explore the underlying neural mechanism for the production of such nasal hyperfunction.

I. Tissue Changes in the Nose in Response to Situational Threats Engendering Conflict

Sustained nasal engorgement with pain in association with resentment, frustration and guilt. Observation 1. A 25 year old physician of Scotch-English extraction, was observed daily 6 days a week for 8 months. He was warm and friendly in his inter-personal relations and aggressive, energetic and self-confident in his approach to his job. His system of security depended predominantly on 3 factors: the approval of his superiors; his ability to be assertively independent in the economic and social spheres; his achievement of a recognized position in competitive society, "success" in his "career".

Shortly after the birth of his first child, his mother-in-law came to visit. The domineering manner in which she dictated the care of the infant and regimented her daughter's convalescence were intensely resented by the subject. He interpreted her behavior as a threat to his position as head of the household and as casting doubt on his judgment as a physician. Soon the situation became intolerable to him. After much misgiving and procrastination, he finally had a "talk" with his mother-in-law, following which she was less aggressive. The subject, though tense, angry and guilty, was gratified to regain his place as head of the family.

During the episode of suppressed resentment there was observed marked sustained nasal hyperfunction (shown graphically in Fig. 1), characterized by hyperemia of the membranes, swelling, hypersecretion and obstruction. These changes were accompanied by restlessness, loss of appetite, flushed face, and a dull, aching "sinus pain" located deep under the bridge of the nose and spreading out over the zygomata (Fig. 2). Following resolution of the difficulty the nasal hyperfunction subsided and pain disappeared.

Comment. Nasal pain was frequently encountered in other subjects during

periods of mucosal hyperemia and swelling occurring in response to life situations engendering conflict, with anxiety and resentment[13]. The subjects were aware, during such periods, of discomfort in both nostrils which at times developed the quality of a burning pain of 1 to 2 plus intensity, increased by forced inspiration to 4 plus intensity. There occurred, usually with the burning pain, a dull aching pain deep under the bridge of the nose of 1

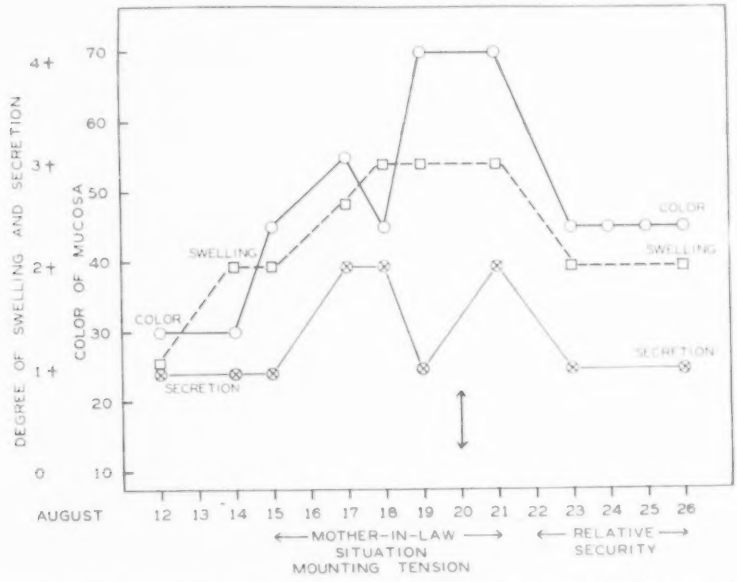

FIG. 1.—Nasal changes during periods of anxiety and conflict regarding the activities of an officious mother-in-law and threat to subject's independence.

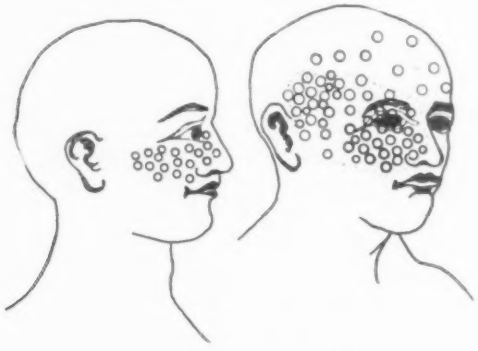

FIG. 2.—Distribution of pain during periods of stress; A, associated with brief periods of swelling and reddening of the turbinates, increased secretion and obstruction predominantly on the right; B, associated with sustained swelling and reddening on the right (during an attack diagnosed as "sinusitis") with photophobia, lacrimation, congestion of the conjunctiva on the right, and flushing of the whole face. There was some intense erythema and "hyperalgesia" over the zygoma.

to 4 plus intensity, which was experienced as well in the orbits, the upper teeth, and along the zygomata. The pain was most often unilateral, occurring on the side of the swollen nasal structures. When the swelling shifted to the opposite nasal cavity, the pain correspondingly changed position. When, in a setting provocative of conflict and anxiety, nasal hyperfunction was marked and prolonged for days or weeks, pain occurred bilaterally over the face in the location described. Pain was intensified by bright lights and a tight collar. It was worse during the working day, increased during periods of stress, and was less intense in the early morning and late evening. When the pain became relatively intense, superficial and deep hyperalgesia developed in areas of spread of pain, along with photophobia and injection of the sclera on the same side. These symptoms were not dependent for their occurrence on demonstrable pathological involvement of the paranasal spaces.

Evidence has been presented elsewhere[18] demonstrating that the ostia, ducts and turbinates in the nose are far more pain-sensitive than are the linings of the sinuses themselves, and are the site of origin for most of the noxious impulses responsible for "sinus headache". Further, noxious stimulation of these intranasal structures caused spread of pain into the areas of the head, as represented in Fig 2. As previously observed in the skin[31], stomach[37] and bladder[19], the swollen, hyperemic mucous membrane of the nose was often found to be accompanied by a lowering of the pain threshold[18].

Nasal Exudate and Pus Cells. Observation 2. The same 25 year old physician described above had presented for evaluation the results of his recent investigations. His senior associate expressed dissatisfaction with the arrangement of the material and was unsympathetic with the formulation. The subject, reacting to this situation with resentment and feelings of frustration and humiliation, again developed nasal obstruction and hypersecretion. (Fig. 3.) The secretion was thick, viscid and gray-yellow in appearance and contained a large number of neutrophils as compared with previous control observations. The neutrophils diminished in number and the nasal hyperfunction subsided one hour after the interview, as the subject became relaxed and regained relative security.

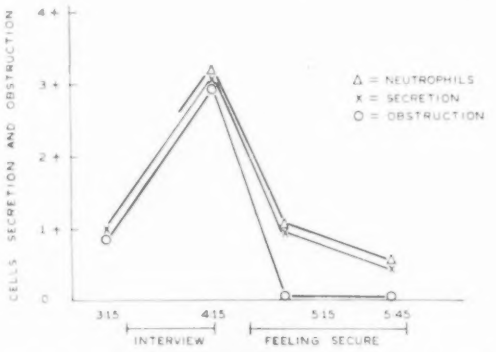

Fig. 3.—Neutrophilic reaction with hypersecretion and obstruction to breathing in the nose accompanying feelings of resentment, frustration and humiliation during interview of a physician with his senior associate.

Eosinophil Response in the Nasal Secretions. Observation 3. A 36 year old white male college graduate and beer salesman suffered from chronic vasomotor rhinitis. During an interview which occurred in a setting of an acute reactive depression, frank weeping ensued on several occasions as he discussed his difficulties with interpersonal

adjustments and his failure to achieve success and stability in the economic sphere. His dominant feelings included resentment, frustration, guilt and humiliation. Accompanying the pronounced nasal hyperfunction (Fig. 4), was: (1) a sharp increase in the number of eosinophils and neutrophils in the nasal secretions; and (2) a rise in the number of eosinophils in the blood from 50 per cu. mm. to 220 per cu. mm. (Fig. 4).

Following the weeping episodes, as the subject became relatively tranquil, nasal

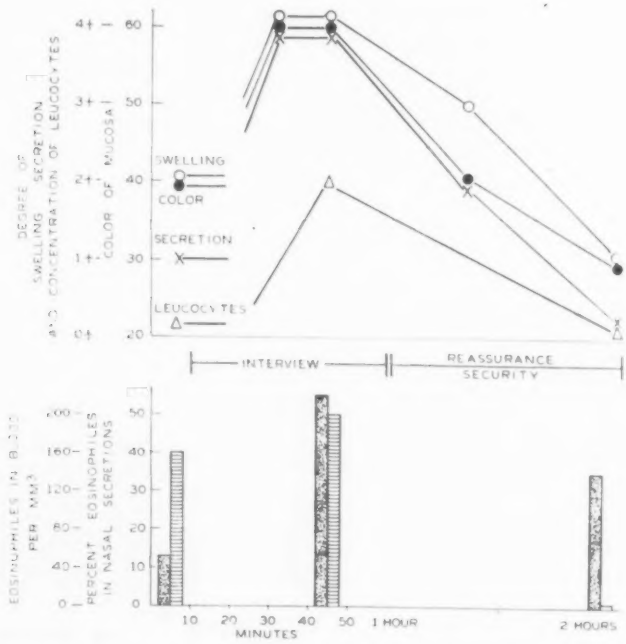

FIG. 4.—Eosinophil and neutrophil reaction in the nasal cavities with nasal hyperfunction and weeping accompanying feelings of resentment, frustration, humiliation, and guilt during an interview with a 36 year old beer salesman. (Stippled bars represent blood eosinophil counts.)

hyperfunction subsided, the phagocytic white blood cells almost disappeared from the scanty nasal secretions and the number of eosinophils in the blood approached the control level.

Comment. Exudation of both neutrophilic and eosinophilic leukocytes has also been observed not only after the inhalation of pollen but following direct noxious stimulation of the nose by ammonia fumes and painful constriction of the head by a tight steel band[12].

From these data and those recorded by the two foregoing observations it would appear that neutrophilia and eosinophilia in the nasal secretions occur in response to various threats and assaults as part of the same broad biological protective pattern of defense which includes hyperemia, swelling, hypersecretion and obstruction in the nose.

Biopsy Evidence of Edema, Engorgement of the Vascular Lymphatic Channels, and Glandular Hyperfunction in the Nasal Mucous Membrane. Observation 4. During a period of good spirits and relative freedom from nasal disturbance the same 36 year old white male described in Observation 3 above was subjected to a vigorous discussion of fundamental personal conflicts. At the outset of the interview the nasal structures were of

relatively normal appearance. The color of the mucous membrane was 40, secretion was minimal and both lower turbinates appeared slightly violaceous. There was 2 plus swelling and obstruction on the right and 3 plus swelling and obstruction on the left. Im-

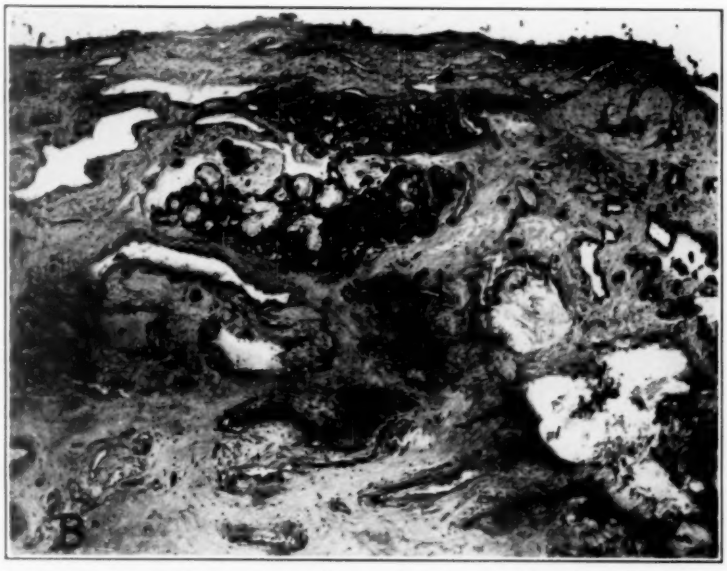

FIG. 5.—Biopsy from the nasal mucous membrane of a 36 year old male with chronic vasomotor rhinitis before and after interview engendering nasal hyperfunction and conflict (See Obs. 4). A. Biopsy of the left lower turbinate obtained before interview when nasal function was within average limits. Section shows low grade chronic inflammation, relatively undilated vascular and lymphatic channels, and compact, quiescent mucous glands. There is no edema of the stroma. B. Biopsy of the right lower turbinate obtained 1 hour after the biopsy in (A) above, at the point of maximal nasal hyperfunction accompanying verge of tears and feelings of conflict. Section shows prominent, dilated vascular and lymphatic channels, active mucous glands containing masses of stagnated secretion, and edema, as indicated by the lighter value of the stroma. (x 200, Masson's Trichrome Stain.)

mediately after this observation a biopsy* was made of the left lower turbinate under local 10% cocaine anesthesia. As shown in Fig. 5A, the section revealed essentially normal mucosal structure with a moderate round cell infiltration. During the next hour, as the subject discussed his lack of success in his job, his inadequate sexual adjustment and inability to assume his responsibilities as a husband and father, and his difficulties with his father-in-law, he became restless and agitated and approached the "verge of tears". His feelings were those of resentment, frustration, humiliation and guilt. At this point, 1 hour after the first biopsy, examination revealed the mucous membrane in the right nasal cavity to be deep violaceous red (70)† with 4 plus swelling, secretion and obstruction. A second biopsy was then obtained under local 10% cocaine anesthesia from the right lower turbinate. As shown in Figure 5B it revealed the mucous glands to be filled with secretion and the vascular and lymphatic channels to be prominent and dilated. The lighter stroma was indicative of edema.

Comment. It then became apparent that when the pattern of nasal hyperfunction, which is designed for short term use, is sustained and intense, pathological tissue changes may ensue. Thus the maintenance of persistent nasal hyperfunction proves a costly and inappropriate way to deal with adverse life situations.

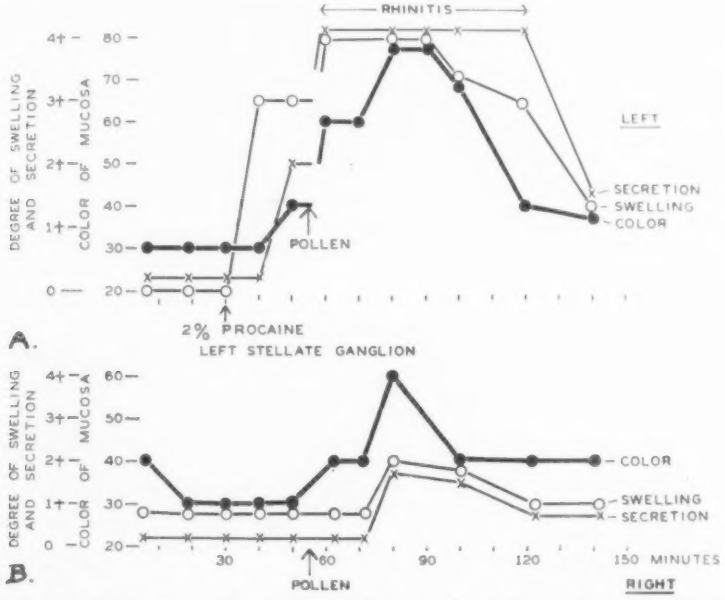

FIG. 6.—A. Hyperemia, hypersecretion and swelling in the left nasal cavity following left stellate ganglion blocks with 2% procaine. B. Production of "hayfever rhinitis" following introduction of 2 mg. mixed rag weed pollen on to the acutely and intensely hyperfunctioning mucous membrane in the left nasal cavity. Note that hyperfunction in the right nasal cavity following introduction of pollen was delayed in its appearance and of low intensity.

2. NEURAL MECHANISMS OF NASAL HYPERFUNCTION IN RESPONSE TO THREATS AND ASSAULTS ON BODILY INTEGRITY. *Nasal Function Following Brief Unilateral Stellate Ganglion Block. Observation 5.* Following suitable control observations on nasal function (Fig. 6), 6 cc. of 2% procaine was injected into the left stallate ganglion‡ of

* We are indebted to Dr. Gervais Ward McAuliffe, Associate Professor of Clinical Surgery (Otolaryngology), Cornell University Medical College, for performing the biopsy and to Dr. Nathan Chandler Foot, Professor of Surgical Pathology, Cornell University Medical College, for the preparation and interpretation of the microscopic sections.

‡ We are indebted to Dr. Bronson S. Ray, Professor of Clinical Surgery, Cornell University Medical College, for performing the surgical procedures.

† Degree of color.

a 58 year old negro male who suffered from seasonal hay fever. Accompanying the other objective signs of the unilateral Horner's syndrome which resulted were hyperemia, swelling, hypersecretion, with moderate obstruction to breathing in the left nasal cavity (Fig. 6).

Comment. This observation suggests that impulses mediated by cholinergic fibers in the greater superficial petrosal nerve are responsible for the production of the pattern of nasal hyperfunction described in this report and is in agreement with the work of other investigators[3,7,8,9].

Effect of Sustained Noxious Stimulation on the Already Hyperfunctioning Nasal Mucosa. Observation 6. At the point of maximal nasal hyperfunction 20 minutes after the stellate block described above (Fig. 6A), 2 mg. mixed ragweed pollen were introduced into each nasal chamber. The response of additional hyperemia, swelling, hypersecretion and obstruction on the left side was intense and dramatic and the symptoms produced in the left nasal cavity were those of "hay fever" (Fig. 6B). In the right nasal chamber, however, the hyperfunction was delayed in its appearance and was not of sufficient magnitude to produce symptoms.

Comment. This experiment indicates that during the phase of intense nasal hyperfunction induced by stellate ganglion block, the functionally altered mucous membrane reacts promptly and vigorously to contact with a noxious agent, culminating in frank manifestations of nasal disease. On the other hand, the introduction of pollen into the functionally intact mucous membrane in the absence of preexisting hyperfunction, even in a known "hay fever" sufferer, induced only a transient hyperfunction which was well tolerated.

Recurrent and Chronic Rhinitis Occurring in a Life Setting Provocative of Conflict, Anxiety, Resentment and Insecurity. From the study of 100 patients with chronic recurrent nasal disorders, it was possible to establish in many a close correlation between the occurence of symptoms and certain life situations giving rise to conflict with anxiety, resentment and frustration. The following case history is a representative example.

Observation 7. A 27 year old married housewife with a long standing history of "nose trouble" complained of nasal obstruction, sneezing and profuse watery nasal discharge most severe during the preceding 7 months.

At the age of 3, her parents died of pulmonary tuberculosis and her childhood under the supervision of a series of responsible but unaffectionate relatives was remarkable for the lack of stability and continuity in care. Aged 5, she was adopted by a "highly educated", driving couple who were enthusiastically interested in the betterment of their community and given to lively arguments, not only about the child's care but about other topics of mutual concern. Also living in the household was an older daughter and a kindly, gentle physician. The latter was the only one who freely gave affection to the patient and he soon became a significant symbol of security to her.

Although her general health was good, the patient had, throughout her childhood, frequent "head colds". Her first serious attack of nasal disease occurred at age 20 when her friend and confidant, the elderly physician, died. She reacted to his loss with feelings of intense grief accompanied by weeping. She felt deserted and became fearful of losing others whom she loved. Again, 1 year later, an exacerbation of nasal symptoms occurred in the setting of a family argument which engendered in the patient intense feelings of insecurity and considerable anxiety and resentment concerning the instability of her home and family. Following this attack she underwent a submucous resection.

She married, with her parents' approval, shortly after her graduation from college, and in the security and tranquillity of her own home she remained free from symptoms. Her first pregnancy, 18 months later, was uneventful and during the antepartum period she enjoyed the unqualified "support" of both her husband and her obstetrician.

The last attack of severe nasal symptoms began during the third month of her second pregnancy when another obstetrician told her that she had "heart trouble", that she would have to be "watched closely", and that her circulatory disorder would preclude the use of general anesthetic during delivery. At about the same time her husband enlisted in the Navy. Symptoms continued unabated throughout the pregnancy. Her labor was

long, the delivery difficult and she became intensely resentful of the obstetrician whom she felt had allowed her to suffer unnecessarily. Two days after her return home from the hospital, her husband reported for active duty and she felt lonely, deserted, frustrated and tearful, and her nasal symptoms became incapacitating.

Examination of her nose in March, 1944, revealed the nasal mucosa to be a deep red color (80) with 3 to 4 plus swelling, secretion and obstruction.

without nasal complaints for more than 3 years. The coincidence of situational threats and nasal disturbances in this patient is illustrated graphically in Fig. 7.

In many of the subjects studied the nasal changes were ultimately associated with chronic infection and polyp formation.

General Comment and Formulation. From the available data, samples of

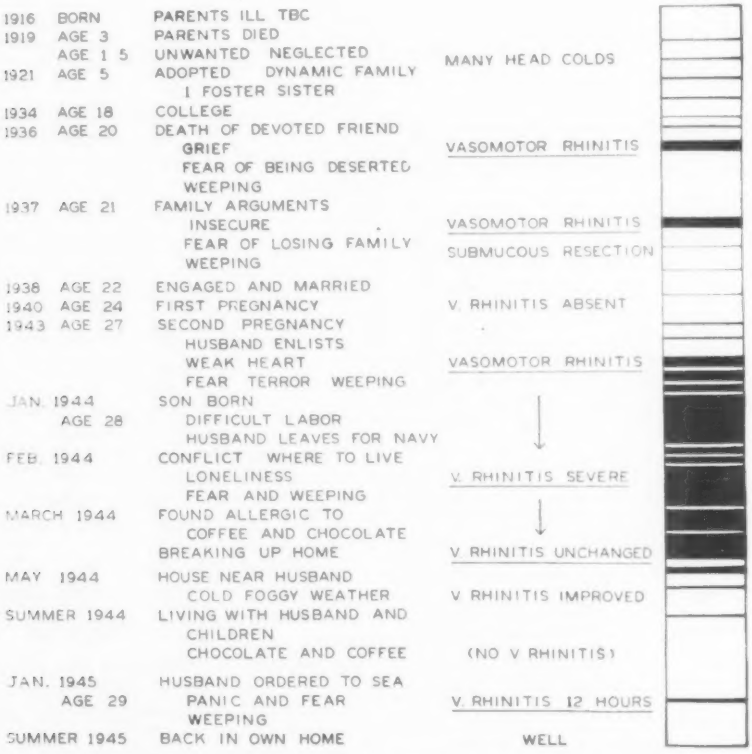

FIG. 7.—Life chart illustrating coincidence of situational threats and nasal disturbances in an insecure, anxious woman. The black bars at the right indicate the occurrence, duration and intensity of troublesome symptoms.

Eventually, during subsequent clinic visits, she was able to relate her fear of desertion to her childhood experiences and these fears to her symptoms. As this understanding was achieved, her nasal symptoms gradually subsided. By January, 1945, she was not only symptom free and effectively fulfilling her role as wife and mother, but her nasal structures were of average appearance—redness 30 to 40, 2 plus swelling, 1 plus secretion and no obstruction. She remained essentially

which have been presented in this communication, it would appear that the nasal hyperfunction characterized by hyperemia of the nasal mucosa associated with turgescence of the erectile tissues in the turbinates, swelling of the nasal mucosa, hypersecretion and obstruction to breathing, constitutes a part of a broad biologic protective

pattern of defense. Since respiration consists of an in and out circulation of air through the respiratory passages, the "shutting out" pattern of nasal hyperfunction thus involves equally a "shutting in". In effect, the individual diminishes his exchanges with his environment and limits the extent of his participation in the situation about him. Thus insulated, he takes in less and gives out less.

Subjects exhibiting this "shutting out —shutting in" pattern of non-participation have been studied[13] and were found to be defensive, insecure, sensitive and dependent individuals who talk with difficulty about relevant personal matters and seldom take positive steps to improve their state. They required a lively show of love and affection on the part of others but were unable to return significant amounts of sympathy, warmth and affection. In many who were deprived of devotion and tenderness in early life, events which threatened such emotional support in later life often induced an exacerbation of the defensive reaction of nasal hyperfunction. Such individuals were quick to react to threatening situations with feelings of intense humiliation and many of their attitudes and behavior patterns were designed to protect their sensitive feelings by "keeping the peace", "avoiding issues" and "doing for others". When their precarious security props were jeopardized, the content of the ensuing state of conflict included in addition to humiliation, intense resentment, frustation and guilt. They were often unable to admit or express feelings of hostility or anger but rather resorted to weeping or aggressive and desperate clinging to that which offered security.

Shutting out, neutralizing and washing away in the nose seems to imply defensive activity at the head end of the organism. During weeping the eyes participate in the pattern. In some patients obstruction of the esophagus and in others constriction of the bronchi have been observed to occur in response to situations engendering conflict with anxiety and nasal hyperfunction[14]. The work of Faulkner and of Stewart Wolf[6,35] provides further convincing evidence that the bronchi and esophagus participate in the shutting out, non-participation pattern of defense. Thus, the respiratory apparatus and upper alimentary tract, the orbital and skeletal muscle structures of the head may act as a unit of function in shutting out, washing away and neutralizing an environment that is literally or symbolically noxious.

The pattern of nasal hyperfunction with hyperemia, swelling, hypersecretion and obstruction, is effective in keeping out of the body dust and irritant gases. It is less effective, however, in protection against blows to the head or situational threats involving interpersonal relations, such as hostility of a parent or marital partner. Indeed, if prolonged, the pattern itself may lead to distress in addition to that arising from a threatening life situation.

Hyperemia, hypersecretion and swelling occurring in a mucous membrane that is already hyperfunctioning can produce pathologic tissue changes. The edematous and chronically inflamed hyperfunctioning nasal mucosa can no longer tolerate or deal adequately with the insults of such noxious agents as pollens or irritant chemical fumes without the advent of additional hyperfunction of sufficient magnitude to induce the signs and symptoms of a "vasomotor rhinitis" and additional tissue damage. Indeed, such an altered nasal mucous membrane soon becomes unable to tolerate the additional hyperfunction induced by such ordinarily innocuous assaults as cold atmosphere, cutaneous chilling, dust or bright lights without symptoms.

Furthermore, as with other ducts and cavities in the body, the presence of chronic obstruction and loculation of secretion in the nasal cavities may favor the invasion and growth of microorganisms. Once it has become established, the infective process can prolong the period of morbid changes in the nasal and paranasal spaces and lead to serious disease and incapacity which may persist long after the precipitating emotional conflict has been resolved.

It is not implied from these observations that all nasal disease stems directly from situations involving difficulties in interpersonal and social adjustments. There are certainly other major factors which set in motion the chain of events described. However, situational threats involving interpersonal and social adjustments occupy a position of importance and may modify the course of the morbid process regardless of the precipitating incident.

Summary. 1. Life situations productive of conflict with anxiety, hostility, guilt and feelings of frustation and resentment were commonly accompanied by nasal hyperfunction with hyperemia, swelling of the nasal mucosa, hypersecretion and obstruction to breathing in the nose.

2. There was also observed an associated pyogenic-like reaction with an increase in the neutrophil and eosinophil content of nasal secretions.

3. Biopsy obtained under these circumstances revealed edema of the stroma, dilated vascular and lymphatic channels and hypersecretion of the mucous glands.

4. Cholinergic impulses to the nasal mucous membranes, probably transmitted by the greater superficial petrosal nerve, are responsible for the production of the nasal hyperfunction.

5. The pattern appears to represent an attempt on the part of the organism to protect itself by shutting out, neutralizing and washing away an environment that is literally or symbolically noxious.

6. Nasal pain of 2 types commonly accompanied the nasal hyperfunction: 1, a burning pain located in one or both nostrils; and, 2, a dull, aching pain deep under the bridge of the nose and often experienced over the zygoma, in and above the eye, in the temple, upper teeth and ear. Infection of the nasal or paranasal spaces was not a necessary prerequisite for pain.

7. When such a pattern is unduly sustained, pathological changes occur which give rise to or prolong troublesome symptoms and, especially when coupled with other noxious threats and assaults, become important to the pathogenesis of chronic nasal disease.

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SERIAL DETERMINATIONS OF PROTHROMBIN ACTIVITY IN PREGNANCY AND THE PUERPERIUM

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Various investigators have found an apparent increase in the prothrombin activity of blood under certain conditions. By means of the 1 stage assay method of Quick,[11] shortened prothrombin times of whole plasma, and more consistently, of diluted plasma, have been reported to occur during the postoperative period,[14] in the course of thrombophlebitis,[15] following coronary occlusion,[10] in the early stage of infectious hepatitis,[12] and after the administration of xanthine derivatives[13] or large doses of vitamin K preparations.[18] Prothrombin assay in pregnancy, by either the 1 stage method or the 2 stage method of Warner, Brinkhous and Smith,[20] has produced conflicting results. Using the 1 stage method, Brambel and Loker,[1] and Norris, *et al.*[7,8] noted acceleration of the prothrombin time, mainly in plasma diluted 1 to 4 and 1 to 8, in parturient women at the time of delivery. Field, Overman and Baumann[4] reported similar findings in rats during the last week of pregnancy, and also noted increased resistance to the prothrombinopenic effects of Dicumarol in pregnant and lactating rats. In studies of pregnant women at delivery, using the 2 stage prothrombin assay, Shettles, Delfs and Hellman[16] found variable results, with the majority showing an increased prothrombin content; Javert and Moore,[5] in a similar investigation, noted reductions below normal in almost all their cases. Thordarson,[17] whose method resembles the 2 stage assay, found a gradual rise in plasma prothrombin content during the course of pregnancy and a decrease to normal levels after the first week post-partum. Of his 112 cases serial determinations were done in only a few. In the present study, changes in prothrombin activity during pregnancy and the puerperium were observed by performing serial estimations on individual patients.

Method. A total of 277 prothrombin determinations was done at various intervals on 62 clinic patients; 3 to 10 determinations (average, 5.8) were carried out in each of 41 women, and 1 to 4 determinations in each of the remaining 21 women. The method used was the 1 stage prothrombin assay of Quick, with modifications introduced by Link and Shapiro; the determinations were done on 12.5% saline-diluted plasma as well as on whole plasma. The details of the method were identical with those previously outlined, and the values for a control group was determined.[2] The range of normal values is indicated for both whole and 12.5% diluted plasma by the broken lines in Fig. 1.

Results. The data are outlined in Fig.

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1. A consistent trend is evident in the diluted plasma prothrombin times of the group as a whole; there is progressive shortening below the normal range, from the third month of pregnancy on, with shortest times appearing in the first few days post-partum. Values obtained several months post-partum were uniformly slightly elevated above normal. The same trend is present in delivery, however, the whole plasma prothrombin times are prolonged. One patient with thrombophlebitis occurring in the first week post-partum and 2 with definite histories of phlebitis in previous pregnancies (but not in the present one) showed no differences from the remainder of the group.

Discussion. The changes recorded here gain added significance because

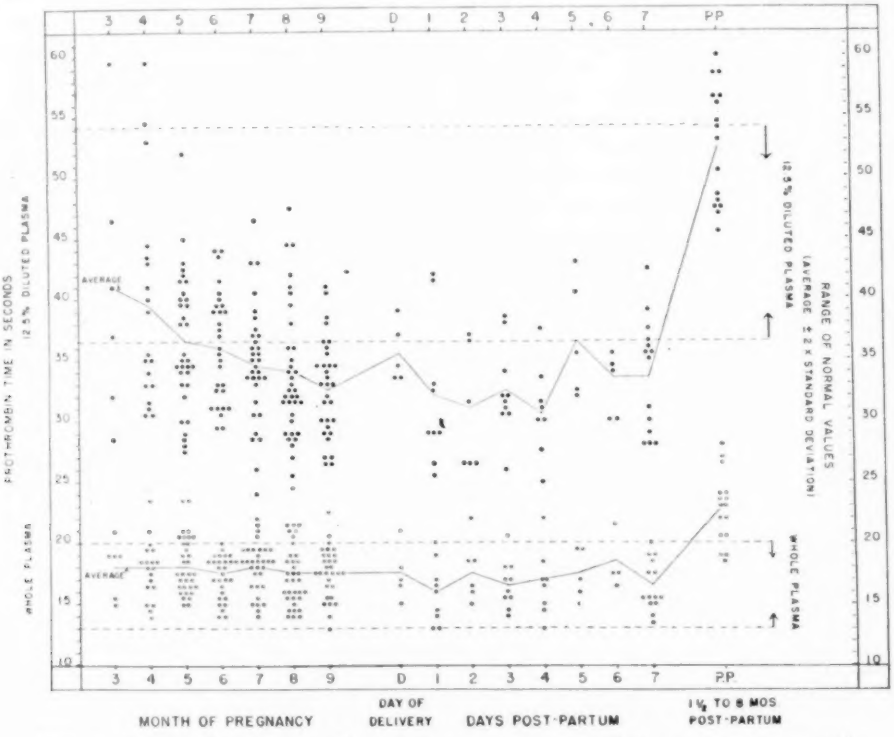

FIG. 1.—Prothrombin times in 62 cases during pregnancy and the post-partum period.
Dots represent individual determinations.
•=12.5% diluted plasma prothrombin time.
°=whole plasma prothrombin time.

the course of serial determinations on individual patients. The whole plasma prothrombin times show no significant alteration in the average values, although there are a few abnormally short times occurring in the latter months of pregnancy and in the first week post-partum. Several months after

of the plasma dilution which occurs toward the end of pregnancy and which of itself would lengthen the prothrombin time. While the mechanism of the further acceleration of the diluted plasma clotting time noted in the first few days post-partum remains to be elucidated, it may be due to the reduc-

tion in plasma volume which follows delivery.

It has been emphasized by several authors that an accelerated prothrombin time by the 1 stage method need not signify an actual hyperprothrombinemia, as variations in other factors in the complex coagulation process may influence the clotting times. Although the plasma fibrinogen concentration increases in pregnancy, and increased fibrinogen under certain experimental conditions may accelerate the prothrombin time (Nitshe, Gerarde and Deutsch[6]), this appears to be insufficient to explain the changes observed here. Further data are needed to clarify this relationship. A plasma activator factor for prothrombin conversion has been suggested (Fantl and Nance,[3] Owren,[9] Ware and Seegers.[19] Variations in this prothrombin activator could affect the results of the 1 stage method, and would tend to be more evident in diluted plasma. Antithrombin substances have been demonstrated in plasma, but there is no data as to their effect on the results of the 1 stage prothrombin assay.

If the observed changes can be taken to signify an increased prothrombin "activity" of the blood, it appears that such an altered state of the coagulation mechanism can exist for a considerable time without resulting in clinical thrombosis.

Summary. In a group of 62 pregnant women, the 1 stage prothrombin determination on 12.5% saline-diluted plasma disclosed progressive acceleration of the clotting time beyond the normal range through the course of pregnancy, and lasting through the first week post-partum. At a later postpartum period, the prothrombin time was somewhat lengthened. The results were similar in individual cases in whom serial determinations were done to those of the group as a whole. No significant changes occurred in the whole plasma prothrombin time.

The authors are indebted to Miss Eleanor Perry for technical assistance in this investigation.

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ANOMALOUS RIGHT PULMONARY VEIN ENTERING THE INFERIOR VENA CAVA: TWO CASES DIAGNOSED DURING LIFE BY ANGIOCARDIOGRAPHY AND CARDIAC CATHETERIZATION

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Anomalous pulmonary veins are occasionally encountered during thoracotomy or at post-mortem examination. The usual anomaly is a variation in number from the expected paired bilateral vessels. Of more interest are anomalous points of entry of one or more pulmonary veins into sites other than the left atrium. These cases may be divided into those with partial shunt of the pulmonary venous return into tributaries of the right heart, and those with total shunt of the pulmonary venous return into the right heart. The latter condition, if uncomplicated by other severe cardiac anomalies, is dependent upon patency of the foramen ovale for life. Actually, very few if any individuals with total shunt survive beyond the first few months of life, and those few who have done so have had associated anomalies allowing free admixture of blood between left and right hearts.

In the literature, Brody[3] and others[1,2,6,8,9,11,13] report a total of 133 cases exhibiting partial (80 cases, 60.1%) or total (53 cases, 39.9%) drainage of pulmonary veins into tributaries of the right heart. The most frequent site was the superior vena cava (42 cases, 31.5%), next the right atrium (21 cases, 15.8%), and the left innominate vein (18 cases, 13.5%). Other sites such as the coronary sinus, a persistent left superior vena cava, the inferior vena cava, the portal vein and the azygos vein accounted for the remaining 52 cases. In only 4 cases (3.0%) did drainage occur into the inferior vena cava.[4,7,12,14] Right pulmonary veins were found to be anomalous about twice as often as those on the left side. Drainage on the left usually was into the left innominate vein or into a persistent left superior vena cava, while on the right, the anomalous vein usually entered the superior vena cava or the right atrium.

Except for 3 cases observed by Brantigan[2] during pneumonectomy, none of the 80 reported cases of partial shunt of pulmonary veins into the right heart was diagnosed antemortem. Of the 4 reported cases of anomalous drainage of pulmonary venous blood into the inferior vena cava, none was diagnosed prior to death. We have observed 2 cases of this anomaly in adult males where modern methods made possible the diagnosis during life and without exploratory surgery. Their clinical reports follow.

Clinical Abstracts. Case 1. A 27-year-old white male was referred for angiocardiography because of a crescent-like shadow in the right lower lung field, discovered on routine preinduction chest roentgenogram in 1943. The patient was asymptomatic; past and family histories were negative. The physical examination was that of an apparently healthy adult male. There were no significant laboratory

findings. Conventional frontal roentgenogram of the chest (Fig. 1A) revealed asymmetry of the chest with the ribs more widely separated on the left. The heart was shifted slightly to the right and its right border appeared prominent. Curving downward through the lower right lung field was a band-like shadow which widened gradually as it descended, paralleling the right atrial border. It then turned inward, becoming obscured at the right cardio-phrenic angle, at which point it measured 24 mm. in width. This shadow could not be identified on lateral examination and was probably superimposed on the cardiac shadow in that projection. An angiocardiogram made in the frontal projection 3 seconds following the injection of contrast material (Fig. 1B) revealed some-

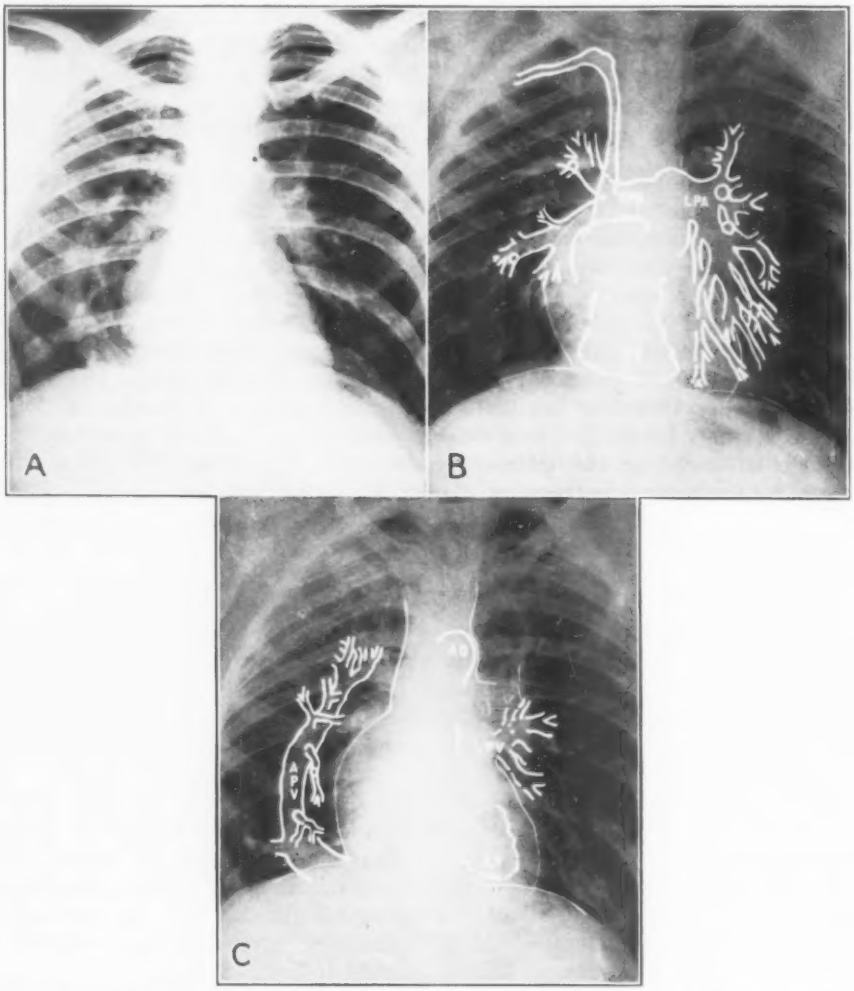

FIG. 1. CASE 1.—(A.) Conventional roentgenogram. Note prominent right heart border and crescent-like shadow in right lower lung field. Left interspaces are wider than those on right. (B.) Angiocardiogram (retouched), made the same day, film exposed 3 seconds after injection. Note slightly enlarged right ventricle, prominent pulmonary arteries on the left as compared to those on the right. Crescent-like shadow in right lower lung field is not opacified. (C.) Angiocardiogram (retouched), made 8 seconds after injection. Left heart and aorta normal. Note opacification of crescent-like shadow, a common vascular trunk draining the right lung to the region of the inferior vena cava.

what enlarged right cardiac chambers. The pulmonary arterial bed was more prominent on the left than on the right side. A film made 8 seconds following injection (Fig. 1C) showed opacification of the left ventricle and the aorta. The left pulmonary vascular bed was unremarkable. The shadow in the right lower lung field was opacified and was seen to consist of a common vascular trunk which received converging vessels from the entire right lung, and which disappeared beneath the diaphragm, apparently entering the inferior vena cava. This network of vessels did not resemble the usual pulmonary veins. The findings were interpreted as evidence of an anomalous common right pulmonary vein draining into the inferior vena cava.

CASE 2. A 41 year old Naval Lieutenant was admitted to the U. S. Naval Hospital, St. Albans, N. Y., for a diagnostic study occasioned by hypertension discovered upon routine examination. He was asymptomatic

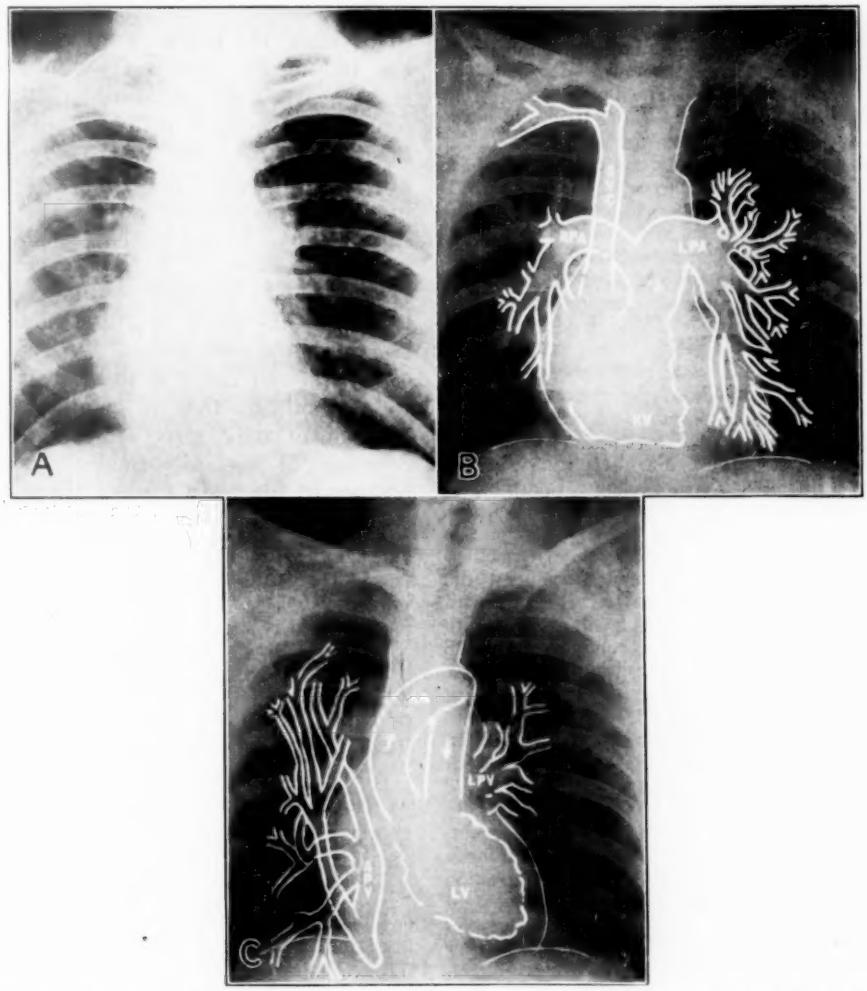

FIG. 2. CASE 2.—(A.) Conventional roentgenogram. Note prominent lower right cardiac border and vague right lower lung field shadows. (B). Angiocardiogram (retouched), made the same day, film made 2½ seconds after injection. Note slightly enlarged right heart, large left pulmonary artery and branches as compared to the right side. (C). Angiocardiogram (retouched), made 8 seconds after injection. Left pulmonary veins are normal. Note common vascular trunk apparently draining the entire right lung and disappearing in the region of the inferior vena cava.

save for mild headaches and fatigue, and the family and past histories were unremarkable. Physical examination revealed an apparently healthy white male save for the finding of blood pressure readings which ranged between 184/120 and 145/105. Laboratory studies were essentially negative save for a slight left axis deviation on electrocardiogram (thought due to the patient's hypertension). Conventional frontal roentgenogram of the chest (Fig. 2A) revealed a dorsal scoliosis with a shift of the heart towards the right. The right cardiac border appeared unduly prominent. On roentgenographic and fluoroscopic examination vague shadows described as exhibiting a "weeping willow effect" were noted in the right lower lung field and interpreted as suggesting a vascular anomaly. For this reason, angiocardiography was performed. A frontal chest roentgenogram exposed at 2½ seconds following the injection of a contrast substance (Fig. 2B) revealed slight enlargement of the right cardiac chambers. The left pulmonary artery was larger than normal and extensive pulmonary arterial vascularity was noted in the left lung field, while the right pulmonary artery was comparatively small and there was definitely diminished vascularity throughout the entire right lung field. A film exposed at 8 seconds after injection (Fig. 2C) revealed opacification of the left atrium, the left ventricle, the aorta and its brachiocephalic branches. A number of unremarkable pulmonary veins in the left lung field entered the left atrium in the usual manner. A network of opacified vascular shadows was seen throughout the right lung field. Individual vessels ran downward, converging at the level of the ninth posterior rib to form a common trunk 18 mm. in width. This vessel pursued a short downward course for 9 cm. where it curved close to the spine at the level of the eleventh rib and abruptly disappeared. A radiolucent area separated this vessel from the left atrium. The configuration of this network did not resemble that of the usual pulmonary veins. A diagnosis of anomalous right common pulmonary vein entering the inferior vena cava was made. Cardiac catheterization was subsequently performed. Oxygen content (vols. %) was determined on various samples of blood with results as follows: (1) Superior vena cava at junction of left and right innominate veins, 11.8, (2) at junction of superior vena cava and right atrium, 13.6, (3) right atrium, 14.6 and 14.4 (two samples taken), (4) inferior vena cava below level of diaphragm, 14.4. These findings were interpreted as showing the ingress of highly arterialized blood into the inferior vena cava and its presence in the right atrium, a confirmation of the angiocardiographic diagnosis. A slightly lower oxygen content in the right atrium than in the inferior vena cava would have been even more convincing evidence in this direction. Further pulmonary function studies are to be done upon this patient at a later date.

Discussion. Anomalous vascular channels causing drainage of pulmonary venous flow into the right heart or its tributaries have been reported in at least 133 cases. Total shunt of the pulmonary venous flow into the right heart is incompatible with prolonged life and is primarily of academic interest, both pathologically and embryologically. Partial emptying of the pulmonary veins into the right heart, however, is compatible with adult life (as in our 2 cases). Hughes and Rumore[9] estimate that less than 50% shunt to the right heart is compatible with normal life.

Both of our cases seem to bear out the hypothesis that a compensatory mechanism may effect a diminished function of the abnormally drained portion of lung. In Case 1 there was definite diminished volume of the right (affected) chest as compared to the left, suggesting that respiratory volume was less on the affected side. In Case 2, the evidence is even more convincing. The left pulmonary artery was larger than normal and the left or "good" lung showed hypervascularity of the pulmonary arterial tree. In contrast, the right pulmonary artery as seen angiocardiographically was small in size and there was definite diminished vascularity of the pulmonary arterial ramifications, as compared to the expected normal and when contrasted with the unaffected side. These changes are probably similar to functional disuse atrophy and hypertrophy in general. In effect, such a patient has what might be referred to as a functional congenital pneumonectomy, since the oxygenated blood

leaving the right lung field is returned to the right heart without having been able to give up its oxygen to the tissues. In both cases, the right lungs, probably histologically unremarkable, are of no functional value to the patients.

Should the shunt be large, it would constitute a definite hazard to the patient, since the right heart would be (theoretically) forced to move a greater than normal minute volume of blood, while the left ventricle would move less than normal. Right ventricular hypertrophy would be expected and has been described.[13] Other undesirable factors may be present as well as a predisposition to right sided cardiac failure. Conant and Kurland[5] cite the case of a patient in whom infection of the anomalously drained lung ran a rapidly fatal course, possibly due to the decreased blood flow postulated above. Disease of the unaffected lung is a doubly serious situation since the anomalously drained lung is of no functional value. Since pneumothorax, atelectasis or surgical removal of the normal lung might bring on sudden death, since the surgical risk is similar to that in a patient with one lung, and since the risk of anesthesia is greater, thoracic surgery should be carefully evaluated.

Extensive pulmonary function studies on individual patients will be necessary in order to evaluate possible therapy for patients such as those reported above. Surgical restoration of the normal anatomical relationships, the ideal solution, would appear to be a more difficult and drastic procedure than is warranted. Similarly, pneumonectomy would seem to be indicated only in the presence or imminence of right heart failure. This is in contrast to the case of arteriovenous fistula of the lung, a more common and probably a more serious condition wherein lobectomy or pneumonectomy is indicated.[10,15] At present, in the absence of criteria for pneumonectomy, conservative management will suffice. It would seem advisable to observe such patients routinely in an attempt to reduce the incidence of pulmonary infection. Patients in whom anomalous vessels drain pulmonary returning blood into tributaries of the right heart from part or all of one lung only, and in whom the condition has produced definite evidence of right sided cardiac strain would seem logical candidates for pneumonectomy. Combined bronchospirometry and cardiac catheterization can be expected to afford much valuable information still lacking.

The diagnosis of anomalous pulmonary veins may be made during life by angiocardiography and confirmed by cardiac catheterization. The findings by catheterization alone resemble those of interatrial septal defect and the differential diagnosis of these two anomalies must depend upon other evidence in most cases. In both of the cases presented here, the clue to ultimate diagnosis was supplied by abnormal shadows of an apparently vascular nature seen in conventional roentgenograms. The thoracic surgeon can be expected to discover anomalous pulmonary venous drainage during thoracotomy in rare cases. Angiocardiography is the most valuable means of diagnosis.

Conclusions. 1. Anomalous drainage of pulmonary veins into the right heart or its tributaries has been discussed from the standpoint of the existing literature, the anatomical findings, the functional abnormalities and the practical considerations referable to certain of these cases.

2. The functional changes consist of: (1) an increased right ventricular output (as compared to the left ventricular output and to a normal right

ventricular output), with secondary right ventricular hypertrophy, (2) compensatory increase of pulmonary arterial flow to the unaffected areas of lung and apparent diminution of blood flow to the abnormally drained areas, (3) comparative functional inactivity of the areas so drained.

3. Two instances of drainage of pulmonary veins from the entire right lung into the inferior vena cava have been presented. These cases were diagnosed during life, utilizing angiocardiography and cardiac catheterization, an achievement not, to our knowledge, previously reported.

Since this paper was submitted for publication, Johnson and McRae[9a] published the report of a patient in whom an anomalous right pulmonary vein apparently drained into the superior vena cava, the diagnosis having been made during life by the methods described in the present report. It is anticipated that further such case reports will be forthcoming.

Thanks are due Drs. John H. Dale and Roy W. Bonsnes for their assistance in connection with the cardiac catheterization study.

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CLINICAL EVALUATION OF DIRECT WRITING ELECTROCARDIOGRAPHY*

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Until recently the action currents detected by all electrocardiographs commercially available have been recorded on sensitized paper in a camera unit. It has been necessary to develop and fix these tracings by the use of appropriate solutions before readings could be made. The inconvenience involved in this procedure has stimulated interest in direct writing electrocardiography so that there are now available on the market several electrocardiographs capable of transcribing the action currents upon a more or less permanent medium without the necessity of subsequently being processed photographically. Thus far the reliability of records thus obtained has been affirmed by the enterprises promoting the sale of these instruments but has not been confirmed by interested electrocardiographers.

In the present study no attempt was made to compare the several machines on the market or to determine the durability of the tracings. Its purpose was rather to evaluate one such direct recording machine† from the standpoint of the accuracy of the records immediately available in comparison with an instrument regarded as acceptable. To this end simultaneous records were obtained through a coupling device transmitting the potentials to a direct writing electrocardiograph and to a standard amplifier type electrocardiograph§ in 25 subjects and through a similar device transmitting the potentials to a direct writing electrocardiograph and a standard string galvanometer type of electrocardiograph¶ in 10 additional individuals.

The coupling unit used for the combination of direct writer and amplifier type electrocardiograph consisted of a lead selector followed by a source of standardizing voltage, the combined output of the lead selector and standardizing circuit being impressed across both electrocardiographs connected in parallel. The coupling unit used for the combination of direct writer and string galvanometer avoided cross interference by converting the electrical impedance of the patient electrode circuit, normally 2,000 ohms, to a few ohms. This was accomplished with a battery-operated vacuum tube amplifier which employed cathode-follower action to impress across a low value resistor the signal applied to the input grids from the relatively high resistance patient electrode circuit. Connections to the electrocardiographs were made in a junction box where 1,000 ohm resistors were inserted in the patient leads of

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† Viso-Cardiette, Sanborn Company, Cambridge, Massachusetts.

§ Stetho-Cardiette, Sanborn Company, Cambridge, Massachusetts.

¶ Simpli-trol, Cambridge Instrument Company, Ossining, New York.

both of the electrocardiographs to simulate the patient electrode resistance encountered in normal use. A lead selector switch was provided in the coupler unit and also a millivolt standardizing switch which served to synchronize all the recordings.

In order to insure that no distortion was introduced into the curves by the use of the coupling device a set of curves was then recorded in 3 individuals each attached directly, first to the direct writer, then to the string galvanometer, and finally to the amplifier type of electrocardiograph without the use of the coupler. Five sets of tracings were thus obtained in these subjects, 2 with and 3 without the use of the coupling device. Although it was impossible to compare identical complexes when the coupling device was not used, the intervals and deflections were then tabulated from what were taken to be representative complexes.

It is to be emphasized that tests made with one direct writing machine are not necessarily an indication of the accuracy of other machines on the market.

Results. In 25 subjects including individuals with normal cardiac mechanisms and various types of cardiac disturbances (anterior and posterior myocardial infarction, paroxysmal auricular tachycardia with block, auricular fibrillation, ventricular premature beats, etc.), the magnitude of the P. Q. R. S., and T waves and the duration of the P-R and QRS intervals, as recorded in the direct writing and the vacuum tube (amplifier) camera type electrocardiograph were identical in the vast majority of cases. In very exceptional instances minimal and insignificant differences (0.01 second) were noted in the duration of the P-R or QRS intervals but in no instance did this constitute the difference between normal conduction on the one hand and auriculo-ventricular or intra-ventricular block on the other. In rare instances minimal and unimportant differences

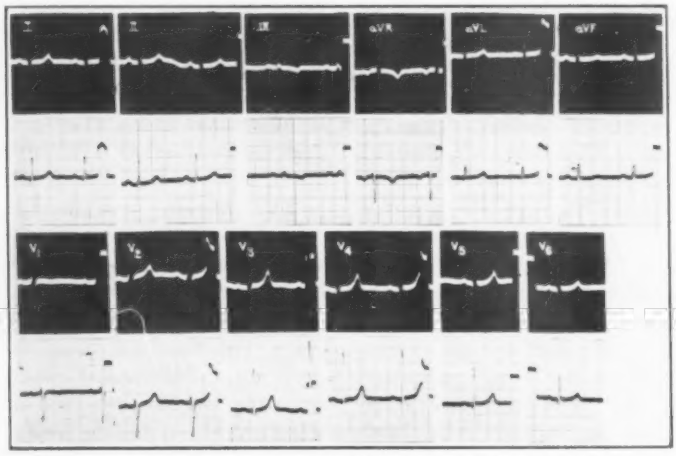


FIG. 1.—Simultaneous tracings taken from healthy young male with camera type amplifier electrocardiograph (white curve on black background) and direct writing electrocardiograph (black curve on white background) through coupling unit. No important differences are noted between the 2 sets of tracings. [This and subsequent figures have been reduced ½ and ¼ from the original photographs submitted, without loss, however, of essential details. For detailed study the size submitted can be adequately brought back with a hand lens.—ED.]

were measured in the height of one or more of the deflections but no changes of importance, such as the loss of a prominent Q or S wave, or important shift of the electrical axis, were noted. In no instance was an elevation or depression of the RS-T segment detected with one instrument and not with the other. There was a superficial difference between the two sets of curves due to differences in the width of the baseline written by each of the machines. Representative comparative tracings are reproduced in Figs. 1 and 2, the former illustrating a normal cardiac mechanism and the latter an antero-septal myocardial infarction. It is to be noted that the R-R intervals were consistently 0.03-0.04 second shorter with the direct writer than the camera machine in Fig. 1 (slower rate) and 0.02 second shorter with the direct writer in Fig. 2. These changes are due to differences in paper speed and are not important.

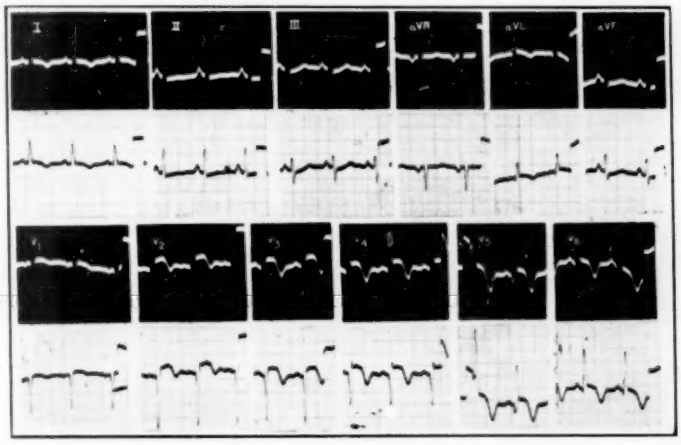


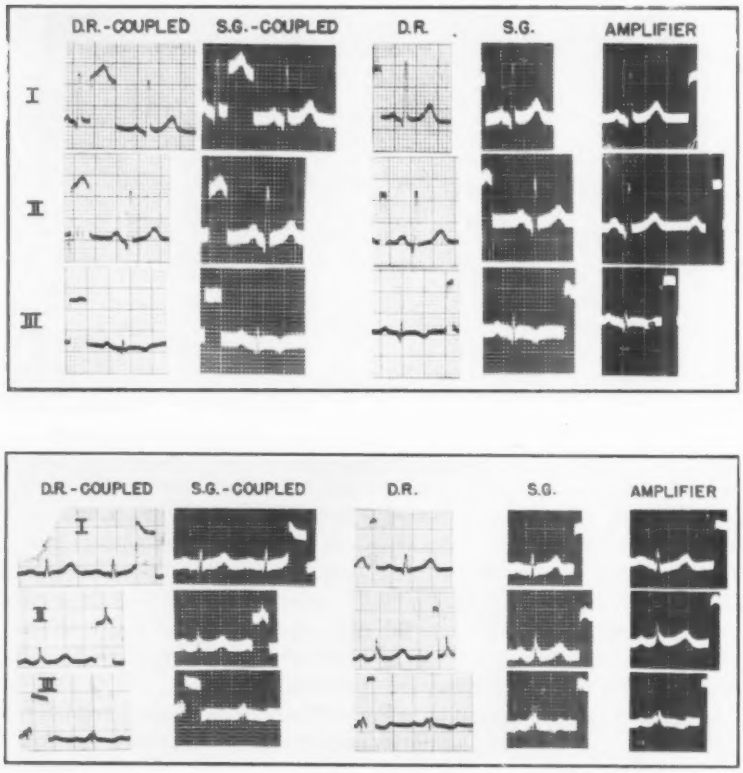
FIG. 2.—Similar tracings taken from 43 year old man with acute antero-septal myocardial infarction. No important differences between the 2 sets of curves.

In 10 additional individuals comparison was made of tracings simultaneously recorded with a string galvanometer and a direct writing electrocardiograph. With the coupling arrangement employed it was difficult at times to standardize so that one millivolt produced just one centimeter excursion in each machine. When appropriate corrections were made for under- or over-standardization, slight differences were measured in the height of these deflections. The differences in the height of the R waves between the string galvanometer and the direct writer were more frequent and somewhat more pronounced than the differences between the direct writer and the vacuum tube type of electrocardiograph. In no case were Q waves or RS-T displacement found with one machine and not with another. In 2 individuals minute S waves were recorded with the string galvanometer and not with the direct writer. No important differences in electrical axis resulted from the slight differences detected in the height of the major QRS deflections.

There were also occasional differences in the duration of the P-R and QRS intervals, the difference usually being 0.01 second, rarely 0.02 second. When a difference was noted the shorter interval was usually recorded by the string galvanometer but oc-

casionally by the direct writer. When a shorter interval was recorded with the string galvanometer, this was due to the fact that the return limb of the R or S wave broke much more sharply with the isoelectric line in the string galvanometer than in the direct writer. At times notching on the downstroke of R, or an embryonic R, as recorded in the string galvanometer, was represented as a slur on the downstroke of R or as a broad, flat S by the direct writer. In no case in the present series did the differences recorded change the interpretation from normal conduction to either auriculo-ventricular or intraventricular block.

Conclusions. A direct writing electrocardiograph operating on the vacuum tube principle was capable of immediately recording tracings faithfully duplicating those obtained with an acceptable camera type vacuum tube (amplifier) electrocardiograph. The occasional differences between tracings obtained with a direct writing and a string galvanometer type electrocardiograph were slight and clinically unimportant and in no case altered the interpretation made.



FIGS. 3 and 4.—Standard lead electrocardiograms in 2 healthy individuals (Subjects 34 and 35) obtained simultaneously with direct writer (1st vertical column) and string galvanometer (2nd vertical column) through coupling unit. The 3rd column shows tracings taken with the direct writer alone, the 4th with the string galvanometer alone and the 5th with an amplifier vacuum-tube electrocardiograph. The measurements obtained are given in Table 1.

TABLE 1.—COMPARATIVE MEASUREMENTS OF INTERVALS AND DEFLECTIONS RECORDED WITH DIRECT-WRITING, STRING GALVANOMETER AND AMPLIFIER TYPE ELECTROCARDIOGRAPHS

Lead	Machine	R-R sec.	P-R sec.	QRS sec.	P mm.	Q mm.	R mm.	S mm.	R′ mm.	S′ mm.	T mm.
Subject No. 34											
	Direct writer—coupled	0.62	0.12	0.10	0.8	1.4	11.4	0	—	—	3.0
	String galvanometer—coupled	0.62	0.12	0.10	1.3	1.4	13.0	0	—	—	3.1
I.	Direct writer	0.70	0.12	0.09	0.9	1.3	12.2	0	—	—	3.1
	String galvanometer	0.67	0.12	0.08	0.9	1.8	11.7	0	—	—	3.0
	Vacuum tube (amplifier)	0.74	0.13	0.10	1.0	1.2	11.4	0	—	—	3.2
	Direct writer—coupled	0.70	0.14	0.07	1.0	1.5	9.9	0	—	—	2.2
	String galvanometer—coupled	0.73	0.14	0.07	1.8	2.2	10.7	0.3	—	—	2.3
II.	Direct writer	0.70	0.14	0.07	1.5	1.6	11.0	0.3	—	—	2.3
	String galvanometer	0.65	0.14	0.08	0.9	2.7	11.6	0.9	—	—	2.1
	Vacuum tube (amplifier)	0.72	0.14	0.08	1.3	1.7	10.1	0	—	—	2.1
	Direct writer—coupled	0.60	0.14	0.08	0.9	0.5	0.3	1.0	1.5	0.5	—0.6
	String galvanometer—coupled	0.64	0.14	0.08	0.9	0.9	0.9	1.9	2.5	1.1	—0.7
III.	Direct writer	0.70	0.14	0.09	0.6	0.4	0.1	1.8	1.8	0.5	—0.6
	String galvanometer	0.66	0.14	0.09	1.0	1.0	0.4	2.1	3.2	1.0	—1.0
	Vacuum tube (amplifier)	0.72	0.14	0.10	0.8	0.6	0‡	1.6	2.0	0.7	—0.7
Subject No. 35											
	Direct writer—coupled	0.68	0.18	0.09	0.9	0.7	4.0	0.3	—	—	2.6
	String galvanometer—coupled	0.69	0.18	0.09	0.8	1.3	4.0	0.7	—	—	2.1
I.	Direct writer	0.68	0.18	0.09	0.8	0.8	3.6	0.5	—	—	2.4
	String galvanometer	6.67	?	0.09	0.6	1.0	3.4	0.5	—	—	2.3
	Vacuum tube (amplifier)	0.80	0.18	0.10	0.6	1.0	3.1	0.5	—	—	2.2
	Direct writer—coupled	0.69	0.18	0.09	0.8	0	3.6	0	—	—	1.5
	String galvanometer—coupled	0.69	0.19	0.08	1.2	0	5.0	0	—	—	1.7
II.	Direct writer	0.72	0.18	0.09	1.3	0	4.1	0	—	—	1.7
	String galvanometer	0.65	0.19	0.09	1.2	0	4.6	0	—	—	2.3
	Vacuum tube (amplifier)	0.78	0.19	0.10	0.9	0	4.3	0	—	—	4.1
	Direct writer—coupled	0.66	?	0.10	0.3	0	1.4	0	2.0	—	—0.4+0.4
	String galvanometer-coupled	0.66	0.16	0.09	0.4	0	2.2	0	2.7	—	—0.4+0.4
III.	Direct writer	0.66	0.16	0.10	0.4	0	1.0	0.8	1.4	—	—0.5+0.3
	String galvanometer	0.67	?0.16	0.09	0.4	0	1.5	0	2.2	0	—0.5+0.6
	Vacuum tube (amplifier)	0.77	0.17	0.10	0.5	0	1.0	0	2.2	0	—0.4+0.3

‡ "Embryonic" R wave

THE COAGULATION TIME OF BLOOD IN SILICONE TUBES*

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Freund[3] showed many years ago that blood will clot much more slowly in a glass tube if that container is first coated evenly with paraffin. It was later noted by Gibbs,[4] who used the various wire loop methods of Inchley,[7] of Dale and Laidlaw,[2] as well as his own, that the type of metal and its state of cleanliness affected the coagulation time. These earlier observations have led to an attempt to explain the varying effects of contacting surfaces, particularly of glass on coagulation time.

The first thorough study attempting to correlate and control contacting surfaces was done by Lampert[10] in Germany and was reported in 1931. He measured the coagulation times in a wide variety of containers under various conditions; the materials included glass, paraffin, resin and other substances. He reported that coagulation times varied in a parallel manner with the surface tension of the blood in relation to the physical container. The substance with the least effect on surface tension was "athrombit," one of the resins, which at 37° C. gave an average coagulation time of about 30 minutes.

In 1942 Lozner and Taylor[12] used a plastic material, "lusteroid," in the form of tubes to determine coagulation times of plasma, and Tocantins[14] used the same material for other studies of plasma. It was apparent that coagulation times were longer with this material. Kadish[9] employed this relatively nonwettable surface for the measurement of the coagulation time of whole blood in an effort to determine whether abnormally shortened times were associated with certain diseases. He used syringes which had an oily protective coating.

Jaques and his co-workers[8] first reported on the use of the new material, silicone, a substance which can be used to coat glass. They found that it was easily applied as a liquid and when dried was smooth, nonwettable, and increased the coagulation time of plasma at room temperatures. The plasma which in ordinary glass tubes formed a clot in 20 to 40 minutes in their experiment was still fluid after 2 to 4 hours in the silicone-coated tubes. These studies indicated that this substance was the most practical of any known for coating needle, syringe and tube, so that venipuncture followed by transfer of blood to a tube could be accomplished with a minimal disturbance of the blood.

Silicone is a clear liquid which does not appear to be changed by standing and may be kept in a capped bottle. It releases a pungent odor of vaporized hydrochloric acid on exposure to the

* Abridgment of part of thesis submitted by Dr. Margulies to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

air. We felt that this material might permit the development of a more accurate method of measuring coagulation time of whole blood. The main advantage, of course, would be the development of smooth, nonwettable surfaces by the coating of silicone. The material used in our work is one of a group of organosilicone compounds, made by General Electric, Schenectady, New York, labelled by them Dri-Film. no. 9987. Jaques and associates,[8] already referred to, worked with centrifuged blood. Since this probably produces significant changes in the coagulation mechanism, we decided to use whole blood without centrifuging for our study. The blood was kept at 37° C.

Method and Procedure. Relatively few materials were needed. We used 10 cc. syringes, test tubes 7 cm. long with an internal diameter of 8 mm., no. 19 and 20 needles. All glassware and needles were scrupulously cleaned and dried before using. The silicone was applied in the following manner. About 200 cc. were poured into a beaker which was placed under a hood. The plunger of each syringe was immersed so that the entire contacting surface was covered by the silicone. With the needle attached, the syringe was then filled and emptied in the silicone solution. To do this the plunger which had already been immersed in the silicone solution was used. The barrel was then filled and the silicone was allowed to run out of the barrel from the open end with the plunger removed so that all of this surface was also covered. Next the tubes to be covered were placed upright in a rack and were filled completely with silicone with syringes which at the same time were being coated. These tubes previously had been calibrated by making a mark on the outer surface at the 1 cc. level. The empty tube was filled with silicone which was allowed to remain in place for 2 or 3 minutes before being poured out again. The tubes were then washed thoroughly with distilled water, at which time pungent fumes appeared. Still wet, they were rinsed in dilute solution of ammonium hydroxide and rinsed again repeatedly in distilled water. The syringes were washed in the same fashion, using the same beaker throughout the whole procedure. Tubes and syringes were then baked for at least an hour at 100° C. in a dry oven. The needles were left on the syringes during this whole procedure and were sharpened after the last rinsing while still wet. They were then placed in individual tubes and sterilized in an autoclave.

On removal from the oven, glass surfaces were seen to be covered by a very thin, smooth, transparent, greasy-appearing material. The syringes worked smoothly after repeated coatings (25 to 30 times in some instances). For the initial coating this whole process was repeated 2 or 3 times. Thereafter, the tubes were recoated once after each use. Syringes were not recoated as frequently and, after 5 or 6 coats were applied, were used for drawing blood about 5 times before a new coat was applied. The continuity of the surface in the syringe was examined by working the plunger and by looking at the surface in a good light. Needles were sharpened after every venipuncture. The silicone was returned to the large bottle after each use but when it became murky was discarded.

Experience with this technic showed us that many little details must be performed meticulously. For example, the needles often become plugged with silicone and have to be cleaned out. The groove in the metal ring of the syringe, where the needle is fitted and locked, may become filled with a gummy padding which can be removed with applicators. Often the small diameter of the syringe, through which the blood first flows on entering the syringe, became plugged with silicone which was removed mechanically.

Blood was drawn for tests from antecubital veins which were filled after occlusion above with a tourniquet. Only a clean venipuncture was used to provide a sample of blood. If one attempt was unsuccessful, the vein was not used but another vein was punctured. Enough blood was always drawn to leave 1 or 2 cc. in the syringe on the assumption that the first portion of the blood might contain more thromboplastin. This portion next to the plunger was not used.

One cc. of the blood was transferred from the syringe to a regular glass tube of the same size as those coated with silicone. Immediately thereafter 3 tubes coated with silicone were filled to the 1 cc. mark and placed in a water bath at 37° C. The remaining portion of the specimen of blood was left in the syringe, which was placed on the butt end of the plunger, so that it remained vertical. Ten minutes after blood was placed into the first glass tube another 1 cc. sample of blood from the syringe was placed into a fresh glass tube. Ten minutes later the same thing was done. Coagulation time of the

blood was measured in each of these tubes from the time the blood entered the glass tube. On a few occasions not enough blood was drawn to complete all of these tests. The blood in the uncoated glass tubes was kept at room temperature and a modified Lee-White[11] coagulation test was done. The tubes were tilted slightly every 30 seconds to determine the end point, which was reached when the blood would no longer flow even though the tube was inverted and tapped gently.

Blood in the silicone-coated tubes was tested as follows. The first tube filled was tilted gently every 5 minutes until signs of clot formation appeared, then every 2 minutes until the end point was reached; the second tube was undisturbed until clotting began in the first tube; it was then tilted every 5 minutes until clotting began and then every 2 minutes until the end point was reached. The third tube was undisturbed until clotting began in the second tube. Then it also was tilted every 5 minutes until clotting began, and every 2 minutes thereafter until the end point was reached. The end point was arbitrarily set at the complete cessation of flow when the tube was inverted. This produced a sharp end point, except in the longest time ranges when it was less definite. Coagulation times were recorded from the time the blood entered the syringe coated with silicone.

Early in the study attempts were made to measure the times at room temperatures, but some coagulation times were found to be as long as 2 or 3 hours. There was a wide variation in end points recorded in the 3 tubes which contained the portions of the same sample. Furthermore, these end points were not definite and in some instances a firm clot never formed. The results reported in this study were all done with the silicone-coated tube placed in a water bath at a temperature of 37° C. At this temperature it was possible to get relatively consistent end points.

Results. *Normal Subjects.* Studies were made on 50 normal individuals. These consisted of physicians, nurses, laboratory workers, college students and hospital employees. Their ages ranged from 18 to 65 years, and all were in apparently good health. There were 33 men and 17 women. The maximal time lost between the venipuncture and filling of tubes was 90 seconds, during which time the syringe was kept at a constant temperature by the body heat produced by the hand in which it was grasped firmly and which covered the whole barrel.

TABLE 1.–SUMMARY OF COAGULATION TIMES IN MINUTES OF NORMAL SUBJECTS

Method	No.	Mean	Standard deviation	Standard error of mean	Range
In glass					
Immediately after venipuncture	50	11.66	2.85	0.40	5-19
10 minutes after venipuncture	46	10.6	2.95	0.44	6-20
20 minutes after venipuncture	46	7.5	2.8	0.41	2½-16
In silicone-coated tube					
Tube 1	50	34.44	8.91	1.26	25-72
Tube 2	50	36.42	8.44	1.19	25-56
Tube 3*	50	38.58	8.20	1.16	25-57

* 88% had coagulation times in silicone-coated tube of 30 minutes or more.

Results of these studies are recorded in Table 1. Attention is first drawn to the readings in the silicone tubes. Since the third was the tube least handled and therefore least affected by undetermined variables, it was the one selected as the most accurate. This one was tilted only after evidence of beginning clot formation was seen in the first two. The average coagulation time was 38.58 minutes (standard deviation ± 8.2 minutes) in the 50 determinations. Times noted ranged from 25 minutes (2 individuals) to 57

minutes (1 individual). The difference in coagulation times between Tubes 2 and 3 was never more than 10 minutes, and averaged 2.2 minutes for the entire group. Interest in single measurements was largely on those near the lower limit for normal. It can be seen that coagulation times of less than 30 minutes in a silicone-covered tube were beyond the usual value for normal blood, and that anything less than 25 minutes might be regarded as abnormally rapid.

In Table 2 are recorded the results of repeated coagulation times in silicone-coated tubes on some of the subjects already observed. Six had 3 tests each on different days. These showed considerable fluctuation and in 2 instances (Subjects 4 and 5) dropped to 30 minutes in one day. None dropped into the range of less than 30 minutes, and all excepting the two noted were well above the minimum established. Five subjects also had repeated tests done on the same day, the first early in the morning, the next just before lunch, the third in midafternoon. Fluctuations were again seen, with a coagulation time of 30 minutes in 1 instance (Subject 6), whereas all

TABLE 2.–REPEATED COAGULATION TIMES ON THE SAME NORMAL INDIVIDUALS

Subject or case	Date	Age, yr. and sex	Silicone-coated tube 1	2	3
			Observations on 3 different days		
1	Nov. 5, 1946	31M	25	30	34
	Jan. 20, 1947		37	39	47
	Feb. 11		37	39	39
2	Jan. 8	26M	30	43	39
	Feb. 12		37	40	54
	Mar. 26		39	45	52
3	Nov. 4, 1946	18F	33	37	41
	Feb. 14, 1947		30	30	32
	Feb. 15		30	39	35
4	Nov. 20, 1946	21F	35	33	36
	Feb. 26, 1947		25	30	30
	Mar. 18		39	46	42
5	Nov. 4, 1946	28M	40	40	45
	Nov. 11		34	30	30
	Feb. 12, 1947		35	41	40
6	Jan. 2	28M	30	30	38
	Feb. 13		30	42	44
	Feb. 26		32	40	50
			Observations repeated 3 times on the same day		
1	9:30 a. m.	31M	37	39	39
	11:00 a. m.		39	42	42
	4:00 p. m.		35	34	35
5	9:40 a. m.	28M	52	52	56
	11:00 a. m.		26	35	35
	5:00 p. m.		35	41	40
6	9:00 a. m.	28M	30	42	44
	11:30 a. m.		25	30	30
	3:55 p. m.		32	40	50
7	9:30 a. m.	19M	32	49	47
	11:00 a. m.		25	43	46
	4:00 p. m.		25	30	32
8	9:35 a. m.	20M	59	54	49
	11:00 a. m.		40	44	45
	4:05 p. m.		38	41	40

of the rest were well above the minimal point.

In the uncoated tubes which were filled with the first sample coagulation times varied from 5 to 19 minutes and averaged 11.6 minutes. All of these were done at room temperature. In the tubes filled 10 minutes later the coagulation times ranged from 6 to 20 minutes and averaged 10.6 minutes in a total of 46 samples, with a standard deviation of ± 2.95 and standard error of mean of ± 0.44. In the glass tubes to which blood was added 20 minutes

TABLE 3.–SPONTANEOUS, INTRAVASCULAR FORMATION OF CLOT

Case	Age, yr. and sex	Diagnosis	Coagulation time, min. In glass tube*	In silicone-coated tubes 1	2	3
9	52M	Ac. thrombophlebitis	11	13	17	23
10†	72M	Chemical (sclerosing) thrombophlebitis	12	45	52	53
11	64M	Ac. thrombophlebitis	12	22	25	28
12	53M	Ac. thrombophlebitis	8	23	28	31
13	40M	Multiple acute thrombophlebitis	11	10	12	12
14	61M	Ac. thrombophlebitis	9		20	26
15	52M	Ac. thrombophlebitis	12	25	24	24
16	52F	Ac. thrombophlebitis	11	25	25	28
17	42M	Ac. thrombophlebitis	10		20	23
18	34F	Ac. thrombophlebitis	8	20	23	23
19	40F	Ac. thrombophlebitis	12	18	22	23
20	18M	Subsided thrombophlebitis	14	40	44	44
21	65M	Ac. thrombophlebitis	14	17	18	19
22	64F	Ac. thrombophlebitis	15	28	30	32
23	61F	Ac. thrombophlebitis	19	20	20	20
24	68M	Ac. thrombophlebitis	13	25	25	29
25	49M	Ac. thrombophlebitis	10	18	25	32
26	61M	Ac. thrombophlebitis	11	19	23	25
27	66M	Ac. coronary occlusion	10	42	45	47
28	37M	Pulmonary embolism	12	38	38	38
29	59M	Pulmonary embolism	11	10	10	12
30	60F	Pulmonary embolism	18	15	16	20
31	47F	Ac. art. occlusion (2 days)	15	48	42	50
32	66M	Ac. art. occlusion (3 weeks)	10	55	45	53
33	54F	Ac. art. occlusion (1 day)	14	14	16	20
34	66M	Ac. art. occlusion (12 days)	9	18	20	22
35	48F	Ac. art. occlusion (6 hours)	?	32	35	30
36	74M	Ac. art. occlusion (4 weeks)	12	30	30	31
Summary of data:						
Mean			11.96			29.21
Standard deviation			2.68			11.27
Standard error of mean			0.52			2.13
Range			8-19			12-53
Number of observations			27			28

† The precipitating factor was the injection of a sclerosing material into varicose veins.

* Immediately after venipuncture.

after withdrawal, the coagulation times ranged from 2½ to 16 minutes with an average time of 7½ minutes (standard deviation of ± 2.8 and standard error of mean of ± 0.41). It should be noted that all testing was done by one person (HM), using as much as possible the same technic throughout. Of the first two, it can be said that there is no significant difference in the time recorded immediately after venipuncture and that noted 10 minutes later, with the blood kept in silicone containers.

Acute Vascular Occlusion. Twenty-eight patients who manifested some clinical evidence of a tendency to thrombosis were observed. These merit close and rather detailed examination. The data on this group are recorded in Table 3. On almost all of them only one study of coagulation time was possible because anticoagulant therapy was used as early as possible. Sixteen had acute thrombophlebitis, which involved veins of the leg. One of these (Case 13, Table 3) also had other veins involved. One patient had thrombophlebitis as a result of the injections of sclerosing solution for varicose veins and 1 patient had passed the active stage of thrombophlebitis, the onset having been 3 weeks prior to the time at which our test was made.

The 16 patients who had acute thrombophlebitis had coagulation times in silicone tubes which ranged from 12 to 32 minutes. For 3 (Cases 12, 22 and 25) of the 16 (18.8%) they were more than 30 minutes; for the others, 1 was only 29 minutes (Case 24), and 1 was only 12 minutes (Case 13), with the remainder lying between these extremes. The coagulation times of 8 of the patients were lower than any observed on the normal subjects. The most rapid, referred to before, was in Case 13 and this was a sample of blood taken from the 1 patient who died. Necropsy revealed that he had carcinoma of the pancreas, complicated by thrombosis in legs, pelvis and abdomen.

Coagulation times in glass tubes at room temperatures on the same group of patients varied from 8 to 19 minutes. The shortest time was noted in Case 12 in which the silicone coagulation time was 31 minutes; the longest time was noted in Case 23 in which the silicone coagulation time was 20 minutes. In Case 10, the case of chemical thrombophlebitis and in Case 20 in which the onset of thrombophlebitis was 3 weeks previously, the silicone coagulation times were within the upper limits of those of the normal subjects.

One case of coronary occlusion and 3 of pulmonary embolism were studied. The patient who had the acute occlusion (Case 27) was so severely ill that he died 2 hours after admission to the hospital. Necropsy was not performed. His silicone coagulation time was 47 minutes. The 3 patients who had pulmonary embolism survived. Two of these had coagulation times in silicone tubes which were well below normal (12 minutes and 20 minutes) and 1 was in the range of normal (38 minutes).

Six patients suffered from sudden arterial occlusion in an extremity, from a few hours to 4 weeks previous to the time the test was made and all were having distress as a result of interference with their arterial circulation. Two of the 6 had silicone coagulation times clearly below normal (20 minutes and 22 minutes); one of these (Case 34) died several days after the test was made, and necropsy revealed thrombotic occlusion of the lower part of the abdominal aorta, whereas the other (Case 33) recovered. Three pursued uneventful courses. One (Case 31) showed no improvement in a week, at the end of which time the affected leg was amputated. The femoral and

popliteal arteries were occluded by thrombi.

Chronic Occlusive Arterial Diseases. There were 23 patients in this group. All came to the Mayo Clinic primarily for treatment of vascular disease. Coagulation times of this group are recorded in Table 4. Ten had thromboangiitis obliterans; 3 of these had silicone coagulation times of less than 30 minutes and 1 of them (Case 42) was a woman. The most rapid coagulation time in silicone-coated tubes in this group (27 minutes) was considerably longer than the most rapid (12 minutes) in the cases of acute thrombophlebitis.

Thirteen patients had arteriosclerosis obliterans. The silicone coagulation times of 2 of these 13 was less than 30 minutes; these 2 (Cases 51 and 57) were kept on dicumarol therapy, and 1 of them (Case 57) will be referred to more extensively in a later paper. He exhibited clinically a thrombosing tendency. The rest of this group of 13 patients had silicone coagulation times within the range accepted as normal.

TABLE 4.–OCCLUSIVE ARTERIAL DISEASES: 23 CASES

Case	Age, yr. and sex	Coagulation time, min. In glass tube*	In silicone-coated tubes 1	2	3
		Cases of thromboangiitis obliterans			
37	52M	14	25	29	38
38	62M	14	26	35	32
39	47M	14	35	38	39
40	49M	15	20	23	29
41	49M	19	20	22	29
42	48F	10	20	27	27
43	36M	10	25	30	34
44	38M	15	40	35	40
45	43M	9	25	40	40
46†	58M	11	30	35	35
		Cases of arteriosclerosis obliterans			
47	79M	11	82	75	72
48†	50M	16	32	30	35
49	74F	15	30	37	38
50‡	60M	11	25	38	30
51	62F	9	22	20	23
52	58M	11	24	28	30
53	62M	13	32	33	34
54	56M	14	33	33	30
55‡	79M	13	70	70	75
56	65M	18	25	35	35
57	48M	10	23	27	27
58	58M	9	35	40	42
59	63M	9	34	41	36
Summary of data					
Mean		12.61			36.96
Standard deviation		2.93			12.53
Standard error of mean		0.61			2.61
Range		9-19			27-75
Number of observations		23			23

* Immediately after venipuncture.
† With diabetes.
‡ With gangrene.

Comment. Bizzozero,[1] when first describing the platelet, postulated that its

disruption and the simultaneous disruption of the leukocyte by various foreign substances precipitated coagulation. Gratia[6] agreed with the explanation that glass caused a disruption of the platelets which released a thromboplastic material, thus initiating a clot. He also stated that certain colloids of the blood were changed by the action of glass and contributed to the same mechanism. The destruction of platelets by contacting surfaces has been commonly considered responsible for this phenomenon. Pickering and de-Souza[13] suggested that fibrinogen has a colloidal protective coat, which is not removed so rapidly in paraffin-lined vessels, but is rapidly dissolved by the action of glass. Gortner and Briggs,[5] who in 1928 measured the electrical charge of various materials, felt that it was possible in theory that glass absorbs positively charged constituents of the blood to its surface in sufficient concentration to initiate coagulation, but they were not actually studying clotting mechanisms. More recently, Lozner and Taylor[12] found that platelet-free centrifuged plasma was capable of clotting, that it acted in a manner similar to platelet-rich plasma. They stated that the effect of foreign surfaces on blood coagulation is essentially independent of the platelet. In the study of Jaques,[8] previously referred to, a poor correlation was found between the number of platelets and the coagulation times and this lent support to the conclusions of Lozner and Taylor.[12]

Tocantins[14,15,16] has shown that blood contains an antithromboplastic substance, anticephalin. He found that when this substance was removed from plasma the clotting mechanism was greatly hastened on subsequent addition of thromboplastin. Various silica substances absorbed the anticephalin, and glass was one of these substances. He attributed the different actions of lusteroid, paraffin, and glass tubes to the variable removal from the plasma of this anticephalin.

It is obvious that a silicone coating on glass inhibits some factor or factors which tend to hasten clot formation *in vitro*. By the same token it is seen that the method involved still introduces environmental influences which disturb the equilibrium needed to keep the blood in its physiologic fluid state. The difference between rapidity of coagulation in glass and in silicone is an indication of the relative crudeness of the test when glass is used; at room temperature this is the difference, in some instances, between a coagulation time of 10 minutes and one of 2 hours or more. One of the primary objects in using such a modification in technic is to discern fluctuation in the normal and from the normal. Contact with glass appears to throw the coagulation system into such violent disarray that more sensitive variations are submerged. Thus, only the most gross abnormality is adequately reflected when the glass tube method is used. It is, therefore, possible that some of the differences in readings from one individual to the next, and in the same subjects, in silicone-coated tubes are the result of accurate measurements and that the same fluctuations that the body exhibits throughout, in other functions, are present in the coagulability of the blood.

It is also likely that a significant error remains even when tubes and syringe coated with silicone are used. A venipuncture, for example, introduces some thromboplastin into the specimen, and it is not known how much this is, or how evenly it is diluted throughout the specimen. No matter how carefully this part of the test is done the exact conditions cannot be consistently repeated. In a series of silicone-coated tubes containing portions of the same specimens

of blood there is a greater difference in end point from one tube to the next as the total times get longer. Probably this increasing error is contributed to greatly by the thromboplastin. Before the water bath was used, and end points were still not definite at the end of 2 or 3 hours, the variation between tubes was as much as 45 to 60 minutes in some instances, although they were portions of one sample of blood. Deliberate introduction of a flaw, such as dirt on the silicone surface, returned the coagulation time to that found in uncoated glass.

The coagulation times in silicone-coated tubes, recorded in Table 1, indicate the effect of gentle tilting every 5 minutes. Although the tilting was done only 5 or 6 times more than in the next tubes, in many cases the clot was formed more quickly. An attempt to eliminate the effects of difference in tilting might be worth while. A mechanical device could conceivably replace manual tilting and thereby increase consistency.

The range of results seen in repeated observations on the same subjects probably represents both normal fluctuations and technical factors. The shortest times produced remained on the low border of the previously established range of normal.

The maintenance of fluidity of the blood in the syringe, left at room temperature, is worthy of attention. It can be concluded that any change in potential coagulability up to 10 minutes is not reflected in the tests done in glass tubes. It is probable that some disruption of platelets is occurring, but this is not marked enough to become apparent by the usual tests. This indicates that there may be some desirable latitude in time spent preparing slides for various studies of morphology if the blood is kept in silicone-coated containers. This could be improved even further, then, if the slides used were also coated and such studies may produce some interesting results.

Also worth noting was an apparent difference in the physical character of the clots formed. The normal subjects, especially those who had blood which clotted in the longer time ranges, produced clots which formed the usual clear end point, but which slid out of the silicone tube in a uniform mass, keeping the shape produced by the contour of the tube almost intact. The remaining drops could be washed away easily. At the opposite extreme was the familiar picture of the clot in the glass which is irregular, tenacious, and has to be removed with a brush. If the silicone-coated tubes were allowed to sit for a few hours, the clot lost its adhesiveness entirely and was virtually floating free in the serum produced around it by retraction. In cases in which the blood clotted more rapidly in the silicone tubes, such as those in Table 3, a clot appeared to adhere more firmly to the wall of the tube although never as markedly as in glass. It is possible that the physical nature of an intravascular thrombosis is also variable, and the concomitant clinical pattern is affected thereby.

The findings on those patients who had acute thrombophlebitis were of particular interest to us. Only 18.8% of this group had silicone coagulation times of 30 minutes or more in contrast with the normal subjects, 88% of whom had silicone coagulation times of 30 minutes or more. It is reasonable to believe that this apparent hypercoagulability contributes significantly to the clotting which occurs as an integral part of the disease. It would be better if these determinations could also be made before the disease makes its presence noted to be absolutely sure that the changes in coagulation time precede the thrombophlebitis. It also should be noted that some of the patients had coagulation times in normal

ranges, despite the presence of definite thrombophlebitis, and that the data for groups of patients who had thromboangiitis obliterans and arteriosclerosis obliterans revealed coagulation times similar to those of the normal subjects. This further substantiates the clinical evidence that no single factor is responsible for the pathologic changes that occur in these diseases.

The method used for silicone coagulation times at present is tedious, especially when results are in the longer time ranges. Its greater accuracy is important when it is valuable to know more about coagulation, whether it is the sole cause of an illness or one of the causes. It would be helpful if some mechanical determination of the end points could be devised to obviate the laboriousness of the tests and the personal factors. If one is interested in demonstrating more rapid times the silicone-covered tubes containing blood could be placed in a water bath, to be checked only 4 times, at the end of 15, 20, 25 and 30 minutes. By this method definite, borderline, and absence of hypercoagulability could be determined.

Summary. A means of measuring coagulation time in containers coated with silicone has been described. Normal times in silicone-coated tubes, established on 50 subjects, ranged from 25 to 57 minutes, with an average of 38.58 minutes. Eighty-eight per cent had coagulation times of 30 minutes or more; therefore 30 minutes is regarded as the usual lower limit of normal.

The effect on the coagulation time of leaving the blood in syringes coated with silicone before it was transferred to glass tubes for testing was recorded on the same subjects. No significant difference was recorded between coagulation times immediately after venipuncture and those obtained on a portion of the same sample left in a silicone-coated syringe for 10 minutes.

Patients with clinical evidence of thrombosing tendencies have been studied and abnormally rapid silicone coagulation times seen in a significant number of them. The patients with acute thrombophlebitis had times of 30 minutes or more in only 18% of those studied; 39.3% of all patients who had spontaneous intravascular clotting had coagulation times of 30 minutes or more.

The silicone coagulation times of nearly all of 23 patients who had occlusive arterial diseases were in the normal range.

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THE COAGULATION TIME OF BLOOD IN SILICONE TUBES IN PATIENTS RECEIVING DICUMAROL*

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In the previous paper[3] we presented data derived from the use of a method for measuring coagulation time of blood in silicone-coated containers. Studies were done on normal subjects and on patients who demonstrated clinically some increased tendency to form intravascular blood clots. Normal coagulation time with this technic, in which the temperature was maintained at 37° C., was from 25 to 57 minutes, with an average time of 38.58 minutes. The technic was found to be dependable in that the end points were clear-cut and the results were reproducible under the variety of conditions outlined in that paper. It was also shown that most patients with acute thrombophlebitis had silicone coagulation times which were abnormally low or at the lowest limits of normal and that this was also true for some of the patients with acute arterial occlusion and with thromboangiitis obliterans.

In the present study it has been our aim to apply the same method of measuring coagulation times to a group of patients receiving Dicumarol. Published reports[1] clearly show that in prothrombin deficiency there is no satisfactory correlation between coagulation times of whole blood in glass tubes and prothrombin times when the coagulation times are determined by the conventional methods and the prothrombin times are measured by either the Quick method or the 2-stage method.

Procedure. Thirteen patients who were receiving Dicumarol were studied. These patients were in two general groups: (1) those in whom intravascular thrombosis had developed; (2) those postoperative patients who had not had intravascular thrombosis but who were treated prophylactically to prevent venous thrombosis and pulmonary emboli. All were given 300 mg. of dicumarol for the initial dose, and were then given either 100 or 200 mg. on any day in which the prothrombin time was less than that time corresponding to the time for 20% normal prothrombin activity (35 seconds in this laboratory).

The prothrombin time was determined by the routine method of this laboratory, the procedure being a modification of the Quick technic.[2] Normal prothrombin time (100% prothrombin activity) was 17 to 19 seconds. It was determined on every day of the study. The sample of blood was drawn in the morning, all of it being taken into a silicone-coated syringe, portions of this specimen being used for both prothrombin time and whole blood coagulation time.

Results. Figs. 1 through 4 are representative graphs with curves of prothrombin times plotted to compare with those representing silicone and glass coagulation times. Generally, the curve of the silicone coagulation times corresponds to that of the prothrombin times.

* Abridgment of part of thesis submitted by Dr. Margulies to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

In each individual studied there were changes in the same direction in the prothrombin time and the silicone coagulation time. As the prothrombin time got longer a similar change occurred in the silicone coagulation time, and the reverse was also true. These changes were not always simultaneous; that is, in some patients the rise in the coagulation time appeared the day after the rise in prothrombin time (Figs. 3 and 4). One patient had a rise and fall in prothrombin time the first 3 days which was not reflected at all in the coagulation times, which went up only with the secondary rise of prothrombin times. To repeat, however, changes in the silicone coagulation times corresponded to changes in prothrombin times in each individual in a very definite manner, as is best illustrated in the figures, but the changes were not always simultaneous.

The data were also examined for all of the subjects at once, rather than for each individual separately. It was found that no correlation existed if all of the prothrombin times were plotted

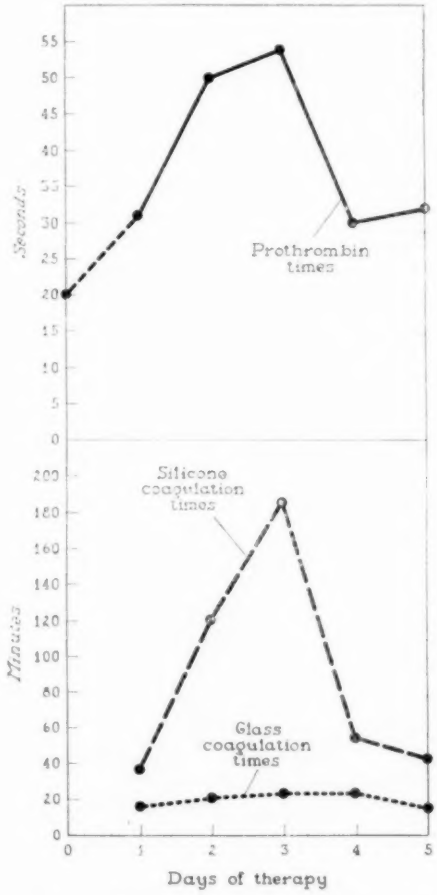

FIG. 1.—Relationship between prothrombin time, coagulation time in silicone tubes and coagulation time in glass. Female patient, aged 32 years, receiving Dicumarol prophylactically beginning 3 days after total abdominal hysterectomy.

against all of the silicone coagulation times. Stated differently, the same prothrombin time in different individuals was associated with widely different coagulation times; furthermore, a change of the same magnitude in prothrombin time on 2 successive days was accompanied by changes of variable magnitudes in the silicone coagulation times on those days. For example, on the fifth day of therapy Patients 1 and 3 had prothrombin times of 32 and 33 seconds, respectively; the corresponding silicone coagulation times were 42 and 120 minutes. Patient 11 had a prothrombin time of 34 seconds on the eleventh day of therapy, and Patient 13 had one of 33 seconds on the seventh day; corresponding silicone coagulation times were 28 and 52 minutes respectively. This last patient was of unusual interest in that he had a high tolerance, apparently, for Dicumarol. It took 7 days and a total intake of 1,000 mg. of the drug to get his prothrombin time up to 33 seconds. Despite the failure to reach the clinically desirable level of 35 seconds, the coagulation time became abruptly longer when the prothrombin time was only at 22 seconds and maintained a level twice as long as its starting point, to which it returned when the prothrombin time dropped back to 18 seconds. Between the third and fourth day of treatment the prothrombin time lengthened by 2 seconds, with simultaneous lengthening of silicone coagulation time

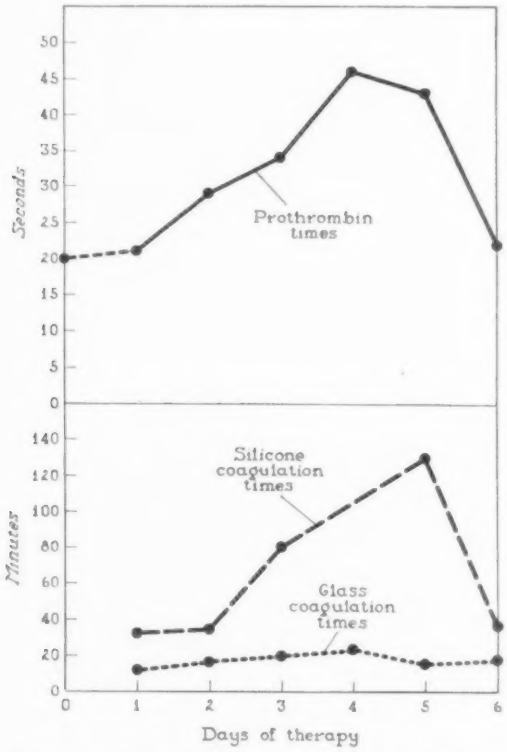

FIG. 2.—Relationship between prothrombin time, coagulation time in silicone tubes and coagulation time in glass. Female patient, aged 65 years, receiving Dicumarol prophylactically beginning 3 days after total hysterectomy.

of 15 minutes. Patient 11 on the same days had a lengthening of prothrombin time of 18 seconds with only a 10 minute prolongation of the coagulation time.

It should be emphasized again that, as the silicone coagulation times became longer (more than 50 to 60 minutes), the degree of error appeared to increase, and it is likely that variations in actual times in the longer ranges cannot be taken at face value. The difference between a coagulation time of 95 and 120 minutes may represent mostly the error factor. This error may be due to the variable amounts of thromboplastin present.

Recordings were also made for the times in glass tubes which were not coated, and these were relatively insensitive to prothrombin changes compared with the silicone tubes. In some instances the anticipated change was reversed.

Comment. These data, derived from patients receiving Dicumarol therapy, show that alterations in prothrombin times are accompanied by corresponding alterations in coagulation times in silicone tubes, but not in glass tubes. The silicone coagulation time is not always changed on the same day as the prothrombin time, but changes are in the same direction consistently enough so that curves plotted to cover several days for both values have similar contours. There is no quantitative correlation which would make it possible to predict from an isolated prothrombin time what would be the silicone coagu-

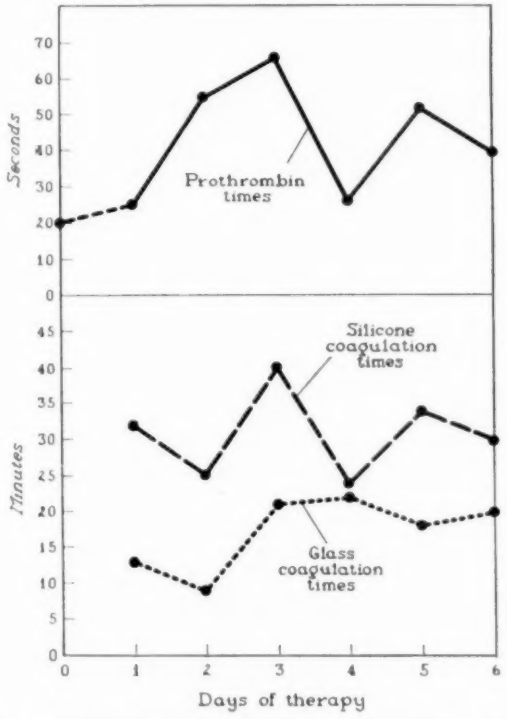

FIG. 3.—Relationship between prothrombin time, coagulation time in silicone tubes and coagulation time in glass. Female patient, aged 45 years, receiving Dicumarol prophylactically beginning 3 days after cholecystectomy.

lation time, as this varies greatly from one individual to the next.

The most immediate observation is that the silicone coagulation time represents a more sensitive measuring device than coagulation times done in glass. In most of the studies there was a change in silicone coagulation time in the manner anticipated from the change in prothrombin time. This was not correspondingly reflected in the glass tube.

In the same patients, however, results suggest that prothrombin time alone may not be the only altered part of the coagulation mechanism which is produced by administration of Dicumarol. This is apparent from the fact that the same levels in 2 patients produce strikingly different coagulation times in silicone. This was especially marked in Patient 13, who resisted Dicumarol so long as judged by the prothrombin time, but in whom ultimately the prothrombin rose to the desired therapeutic level. The other factor (or factors) probably involves the rapidity of conversion from prothrombin to thrombin. One could explain these differences if one assumed that Tocantins' anticephalin substance[6] remained in the silicone-coated system, but was removed by the technic used in the prothrombin determination. This would delay the conversion of prothrombin to thrombin, giving a longer coagulation time.

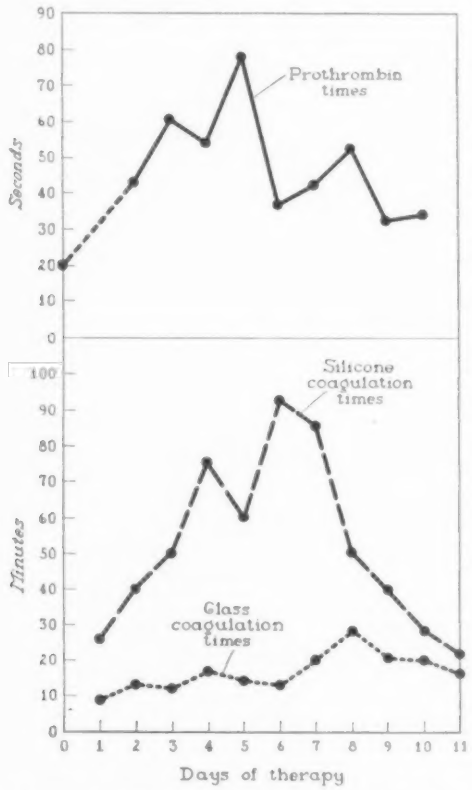

FIG. 4.—Relationship between prothrombin time, coagulation time in silicone tubes and coagulation time in glass. Male patient, aged 61 years, who had had acute thrombophlebitis after abdominoperineal resection. Administration of Dicumarol was begun immediately.

There may, contrariwise, be a substance which acts to hasten that conversion, giving an opposite action to that of the anticephalin. The occasional delay in the effect of Dicumarol on the coagulation time in silicone tubes as compared with its effect on the prothrombin time might then be due to the persistence of such an unknown factor, which eventually is exhausted or depressed by Dicumarol. Wright found evidence to indicate that platelets are more adhesive in the presence of glass, thus hastening coagulation, and Spooner and Meyer attributed at least some of the effect of Dicumarol to a lessening of this adhesiveness. The occasional rare individual who may form a thrombus despite a prothrombin time of 35 seconds would be one who converts even the smaller quantity of prothrombin in such a rapid manner as to produce a clot.

Since this work was done Moloney, Murphy and Harrington have shown a similar correlation between coagulation times in silicone-coated containers and prothrombin blood levels reduced by the administration of Dicumarol.

Summary. 1. Thirteen patients receiving Dicumarol were studied. It was found that the changes in prothrombin time in these patients were associated with corresponding changes in the coagulation time in silicone tubes. Glass tubes used to measure coagulation time in the conventional way did not show these changes.

2. The change in silicone-tube coagulation times was often not simultaneous with the change in the prothrombin time. Possible reasons for this lag are discussed.

3. The relationship between prothrombin time and silicone coagulation time varied from one individual to another. The same prothrombin time in several subjects was accompanied by widely different coagulation times, so that it was not possible to correlate directly the prothrombin time of the patients studied with the silicone coagulation time that they manifested. Change in prothrombin time was, however, accompanied by alteration in coagulation time which was consistently predictable in direction if not in magnitude.

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A HEMATOLOGIC AND ELECTROPHORETIC STUDY ON BLOOD REGENERATION IN DOGS SUBJECTED TO REPEATED PHLEBOTOMY

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Studies by McKibbin and coworkers[9] have shown that dogs receiving a highly purified ration supplemented only with synthetic vitamins are able to regenerate hemoglobin rapidly following an extended series of bleedings. Dogs rendered anemic and hypoproteinemic by dietary means and hemorrhage invariably regenerate hemoglobin more rapidly than plasma protein on a variety of dietary regimens.[12,15]

The present investigation was undertaken to determine the ability of dogs with different dietary backgrounds to regenerate blood components when bled repeatedly over a period of several months.

Materials and Methods. Three dogs were used in these experiments. One had been maintained on a purified diet, No. 620†[13] supplemented with vitamins and 5% dried beef liver for 2 years. Another had received the same purified diet and vitamins without the liver supplement for the same period of time. Hematologic studies, conducted on these 2 dogs since they were given the experimental diets at weaning, revealed no abnormalities. They had, however, shown an impairment in ability to excrete bromsulfalein. The third dog was selected from our stock colony and had been fed a mixed diet consisting of Gaines' dog meal, fresh horse meat and milk. During the course of bleeding the 3 dogs were continued on the same diets *ad lib.* The average daily food consumption was about 200 gm. In addition, daily iron supplements in the form of ferrous sulfate, were given: 20 mg. for the first month, followed by 50 mg. for the remainder of the test period. The total amount of iron, including that in the diet, which each dog received, was approximately 1.4 gm.

Each dog was bled by jugular vein puncture a total of 33 times (100 to 200 cc. taken about 3 times weekly) over a period of 2½ months. The volume of blood removed from each animal during this period totaled approximately 4850 cc. or about 5 times the original blood volume. This quantity of blood had a hemoglobin content of about 372 gm., equivalent to 1.24 gm. of iron.

At each bleeding, determinations were made of erythrocytes, hemoglobin, hematocrit, total and differential leukocytes, plasma fibrinogen, serum protein and albumin-globulin ratios. Estimations of reticulocyte and platelet numbers, prothrombin times, icteric indices and electro-phoretic components of plasma were made less frequently. Hemoglobin was determined colorimetrically in an Evelyn colorimeter. The quantity of hemoglobin regenerated was calculated from the difference in total hemoglobin in each animal between blood withdrawals. The total circulating blood volume was assumed to be 8% of the body weight.[9,10]

Prior to electrophoretic analysis the plasma samples were diluted 3 fold with barbiturate buffer and dialyzed at low temperature for periods ranging from 2 to 6 days in Visking

† Diet 620: Casein "Vitamin free" Labco, 30.0; Dextrose, 41.0; Crisco, 21.0; Corn oil, 0.15; Salt Mixture No. 1 U.S.P. XI, 3.0; Bone Ash, 2.85; Cod liver oil, 2.0. Daily Vitamin Supplement—oral: Thiamine, 1 mg.; Riboflavin, 1 mg.; Pyridoxine, 1 mg.; Nicotinic acid, 20 mg.; Calcium pantothenate, 40 mg.; Choline chloride, 200 mg.; Inositol, 200 mg.; Alpha tocopherol, 25 mg. weekly.

TABLE 1.—HEMATOLOGICAL AND BIOCHEMICAL CHANGES IN DOGS BLED REPEATEDLY.

Dog No.	Diet	No. of bleedings	RBC	Hb	Hcrit	MCV	MCH	WBC	Total gm. Hb removed	Total gm. Hb regenerated	% Hb regenerated	Plasma protein gm. %	Fibrinogen mg./100 cc.	Wt.
203	620	0	6.11	13.0	50.0	81.6	21.2	9,880	—	—	—	6.4	290	14.0
		12	4.71	9.4	41.0	87.0	19.9	11,840	155.0	103	66.5	6.0	330	13.8
		24	4.02	5.0	25.0	62.2	12.4	11,280	287.9	199	69.3	6.2	330	12.4
		29	3.25	4.8	22.0	67.8	14.8	12,880	336.5	236	61.2	—	—	11.5
		33	3.11	4.6	19.5	62.7	14.8	14,320	369.9	273	73.8	6.1	395	11.1
204	620	0	6.50	13.6	49.0	75.3	20.9	11.520	—	—	—	6.3	200	11.5
	plus	12	4.5	8.6	32.0	71.0	19.1	7,920	155.9	109	69.9	5.9	350	11.4
	liver	24	4.07	5.9	29.0	71.3	14.5	6,360	279.9	202	72.1	6.6	540	10.5
		29	3.77	5.7	24.0	63.6	15.2	6,400	333.0	233	69.9	—	—	10.3
		33	2.94	5.0	17.0	58.0	17.0	13,520	365.2	288	70.6	6.2	445	10.0
587	Stock	0	6.89	14.5	50.0	72.6	21.1	12,920	—	—	—	5.7	210	11.2
		12	4.67	9.1	37.5	80.0	19.5	14,480	156.0	76	48.7	4.7	240	11.3
		24	4.3	6.3	29.0	67.5	14.7	13,240	285.7	182	63.7	4.7	210	11.1
		29	3.66	6.5	27.5	75.2	17.8	12,680	347.0	230	66.3	—	—	10.9
		33	3.41	5.2	20.0	59.0	15.2	10,640	384.0	256	66.7	4.5	230	10.6

tubing against 2000 ml. of the same buffer mixture. The electrophoresis experiments were carried out by means of the Tiselius apparatus[14] in an analytical cell of the Tiselius-Longworth type[8] of 11.0 ml. capacity at 1.1°C., for a period of 240 minutes. The buffer consisted of 0.1 N sodium diethylbarbiturate and 0.02 N diethylbarbituric acid, pH 8.6, as recommended by Longsworth.[8] The Schlieren scanning method of Longsworth[7] was used to record the refractive index gradients in the cell. The percentage composition of the electrophoretically separable components was calculated from planimetric measurements of the descending boundaries, following enlargement of the records by projection and appropriate extrapolation. The patterns are, as a rule, rather complex and not completely resolved.[1,2,16]

Results. Table 1 shows some of the pertinent hematological and biochemical data obtained. All dogs showed a loss of body weight. The frequent bleeding of the animals was sufficiently severe to produce a progressive decrease in hemoglobin, erythrocyte, and hematocrit values. Nevertheless about 70% of the hemoglobin removed at each interval was regenerated. There appeared to be no significant difference in the ability of the dogs on the different dietary regimens to make up hemoglobin lost through hemorrhage. The data show the development in all 3 animals of a microcytic, hypochromic anemia. Dog 204, which received the purified diet supplemented with dried liver, suffered a decrease in leukocyte count within 2 weeks. This low count persisted throughout most of the experimental period but returned to normal after the 30th bleeding. All animals showed a slight relative decrease in lymphocytes and a corresponding increase in neutrophils during the last month of treatment. No differences between animals occurred in reticulocyte and platelet counts, in prothrombin times or in icteric indices.

Occasionally during the course of the experiment the blood was noted to clot more rapidly than usual. This irregular finding could not be correlated with prothrombin values or platelet counts determined at the same intervals.

Two dogs were able to regenerate quite readily the plasma protein which was removed. The third animal, given the stock diet, suffered a decrease in this blood component early in the experiment from which it did not recover (Table 1). Plasma fibrinogen levels gradually increased in both animals maintained on purified diets. Since these animals had also shown at the onset of test an inability to excrete bromsulfalein rapidly, the elevated fibrinogen values suggested the existence of hepatic damage. Examination of histological sections of liver revealed the validity of this contention in one of the dogs. The liver of this animal, No. 203, showed centrolobular atrophy, necrosis and fatty degeneration. Biliary stasis was also evident in the central areas of the lobules. Large masses of iron-positive pigment were present throughout the liver. The spleen of this animal also contained considerable iron. The second dog (No. 204) fed the purified diet, likewise had stainable iron in liver and spleen.

The rapidity with which hemodilu-

TABLE 2.–HEMODILUTION AND REGENERATION AFTER WITHDRAWAL OF 200 CC. OF BLOOD.

	Dog No.	Time Interval 0	15 min.	1 hr.	6 hrs.	24 hrs.	48 hrs.
Serum	203	6.0	5.6	5.15	5.35	5.7	6.1
protein	204	6.5	5.75	5.7	5.3	5.7	6.2
gm. %	587	4.6	4.15	3.9	—	4.25	4.5
Hematocrit	203	22.0	21.2	21.0	19.0	14.0	19.5
vol. %	204	21.0	20.0	19.5	17.0	16.5	18.0
	587	22.0	22.0	20.0	—	17.0	20.0

tion occurred following removal of blood was studied immediately after the 32nd bleeding (200 cc.). Table 2 shows that in all three dogs both serum protein levels and hematocrits decreased within 15 minutes to 1 hour after phlebotomy. The serum protein levels were increasing by the 24th hour and were essentially normal by the 48th hour. On the other hand, the hematocrit values were lowest at the 24th hour and had not yet attained the base line values at the 48th hour. These data indicate that hemodilution occurs rather rapidly after withdrawal of blood and that the serum protein tends to be replaced at a more rapid rate than the erythrocytes.

Electrophoretic patterns obtained in these dogs initially and finally after 32 bleedings are shown in Figure 1. The plasma protein spectrum as determined by electrophoretic analyses is recorded in Table 3. At the onset of the test the dog getting stock diet had a higher proportion of albumin and a lower proportion of globulin than the dogs receiving purified diet. The lower proportion of globulin was due primarily to the beta-2 and gamma components. During the course of bleeding, the dog on purified diet without liver showed an increase in albumin and a decrease in total globulin whereas the other 2 animals showed the reverse effect. An increase in alpha-3 globulin and in

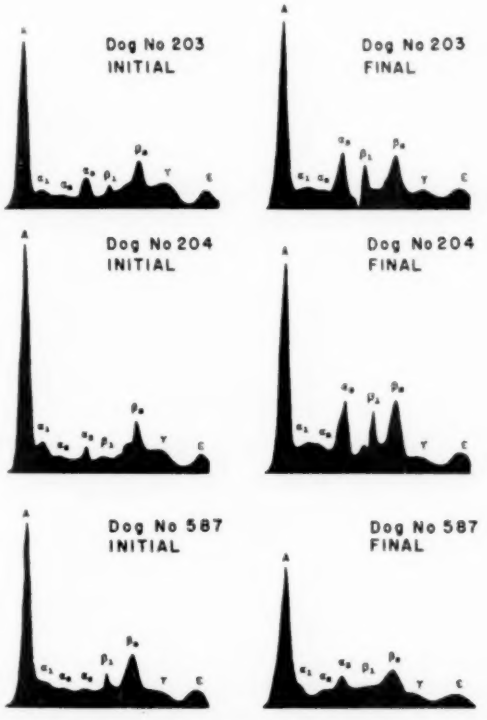

FIGURE 1.—Electrophoretic patterns of dogs obtained before and after 32 bleedings. The diets fed to the dogs were: Dog 203—Diet 620; Dog 204—Diet 620 plus liver; Dog 587—Stock diet. Note the increase in albumin (A) in dog 203 and decrease in this fraction in dogs 204 and 587. In general the dogs show a relative decrease in gamma globulin and increases in the beta-1 and alpha-3 globulin fractions of the plasma.

TABLE 3.–ELECTROPHORETIC ANALYSES OF PLASMA PROTEIN OF DOGS SUBJECTED TO REPEATED PHLEBOTOMY.

Dog No.	Diet	No. of bleedings	Albumin	Total Globulin	Globulin Fractions $\alpha 1+2$	$\alpha 3$	$\beta 1$	$\beta 2$	γ	A/G Ratio
203	620	0	37.7	62.3	12.5	9.6	5.7	20.7	13.8	0.61
		24	44.7	55.3	15.2	7.3	10.8	12.0	10.1	0.81
		32	41.7	58.3	12.9	13.0	9.0	15.4	7.9	0.72
204	620 + liver	0	41.9	58.1	15.0	6.2	7.7	17.7	11.5	0.72
		24	39.1	60.9	15.6	14.3	8.7	17.0	5.4	0.64
		32	37.0	63.0	13.3	14.6	11.2	17.1	6.9	0.59
587	Stock	0	50.2	49.8	12.2	6.0	7.6	15.8	8.2	1.01
		24	42.7	57.3	17.5	7.9	16.0	10.3	5.6	0.75
		32	48.1	51.9	5.6	11.2	11.4	17.1	6.6	0.93

Total protein is taken as 100% and each protein component is indicated as a fraction thereof.

beta-1 globulin§ occurred in all 3 dogs while the gamma globulin decreased. Following bleeding the dog on purified diet without liver showed a decrease of beta-2 globulin. The dog on stock diet showed an increase in alpha 1+2 globulin and later a decrease in these fractions. As a consequence of the foregoing changes in albumin and globulin the albumin-globulin ratio became larger in the dog on purified diet without liver but smaller in the other dogs.

A comparison was made of plasma albumin-globulin ratios determined on 6 samples of dog blood by: (a) electrophoresis, (b) Howe's salt fractionation method[5] and (c) the methanol method of Pillemer and Hutchinson.[11] The latter two methods gave results consistently higher than the first method (Table 4). This is in contrast to Pillemer's finding that in *human* serum there is better agreement between the results of electrophoretic analysis and his alcohol method of fractionation than between either of these two techniques and the salting-out method of Howe. However, we think that this point deserves fuller study in dogs before definite conclusions can be drawn.

Discussion. No striking differences were observed in the ability of dogs receiving different diets to regenerate hemoglobin following a series of rather severe bleedings. The lack of folic acid, p-aminobenzoic acid and biotin in the diet of one dog had no influence on

TABLE 4.–COMPARISON OF ALBUMIN-GLOBULIN RATIOS IN DOG PLASMAS AS DETERMINED BY DIFFERENT METHODS.

Dog. No.	Bleeding No.	Albumin-Globulin Ratio: Electrophoresis	Na_2SO_4 (Howe)	Methanol (Pillemer)
203	1	0.61	1.0	1.1
	24	0.81	1.5	1.95
204	1	0.72	1.7	1.5
587	24	0.75	1.5	—
	32	0.93	1.25	1.6

§ The designation of the various protein components observed in dog plasma is not uniform in all laboratories. The reason for this divergence must be sought in varying degrees of resolution of the dog plasma pattern by different investigators and also in the fact that other authors have labeled as "fibrinogen" the component designated as $Beta_2$-globulin in this paper, although it is evident that only a *fraction* of this electrophoretic component can actually consist of fibrinogen[16]. This component should perhaps be designated [$Beta_2+\phi$] rather than simply $Beta_2$ or ϕ. If due allowance is made for the difference in terminology, the present data appear to be essentially in agreement with those reported by Zeldis *et al.*[17]

blood regenerating capacity. Michaud and associates[10] have shown that dogs on a purified diet, without folic acid or biotin (and even with succinylsulfathiazole added) are capable of adequate hemoglobin regeneration after profound exsanguination.

Two of the 3 dogs quickly replaced the total plasma protein removed. The third animal, while inefficient in this respect, nevertheless had, after the series of bleedings, about 70% of its original plasma protein level. On the other hand, the final hemoglobin levels of the dogs after bleeding were only about 35% of the original values. Thus plasma protein regeneration apparently took precedence over hemoglobin regeneration. This is in contrast to the condition which prevails in anemic, hypoproteinemic dogs in which hemoglobin is regenerated in preference to plasma protein.[12,15] Whipple, Robscheit-Robbins and associates,[12,15] however, provided more iron in the diet of their dogs than was given in the current experiments. Our dogs each received about 1.4 gm. of iron during the experimental period in which an average of 1.24 gm. was removed as hemoglobin. Iron intake, therefore, may have been the prime factor limiting hemoglobin production. However, since only about 0.9 gm. of iron could be accounted for in the regenerated hemoglobin and since stainable iron was observed in the livers and kidneys of 2 dogs, there remains the possibility that faulty utilization of iron contributed to the development of the microcytic hypochromic anemia.[4]

Although total plasma protein concentrations were regained completely or almost so in the dogs between bleedings, the relative concentration of their individual electrophoretic components showed alterations. Zeldis and Alling[16] have observed that after a single acute depletion of plasma protein by plasmaphoresis in dogs the electrophoretic pattern may be disturbed for as long as 2 to 3 weeks after the initial total protein level has returned to normal. In dogs so depleted plasma globulin restoration proceeds more rapidly than plasma albumin restoration. An increase in beta globulin and fibrinogen has been observed in dogs also with severe vascular disease[6] or hepatitis and cholangitis.[16]

Our data, showing that albumin-globulin ratios are lower when determined by electrophoresis than by Howe's method, agree with those of Chow and associates[1] in dogs and Dole and Braun[3] and Deutsch and Goodloe[2] in humans. Chow believes this finding is due to incomplete separation of the globulins from albumin by the method of Howe.

The 3 dogs used in these experiments exhibited a slight but continued weight loss as a consequence of repeated exsanguination. This indicates that the protein stores of the body were drawn upon for regeneration of blood components so incessantly that their replacement by synthesis from ingested food became inadequate.

Summary. Repeated phlebotomy in adult dogs, maintained on diets containing 25 to 30% protein resulted in the development of a microcytic, hypochromic anemia. No differences, ascribable to the dietary regimen, were observed in the ability of the dogs to synthesize hemoglobin.

After a single withdrawal of blood, hemodilution occurred within one hour. Serum protein levels were essentially normal 48 hours later, but hematocrit values were still depressed.

Throughout the course of bleeding, plasma protein production took precedence over hemoglobin production. The possibility exists that this condition may have been due, in part, to iron lack or faulty iron utilization.

As a result of bleeding, an increase in total globulin and a decrease in

albumin was observed in a dog on a purified diet supplemented with liver and in another fed a natural stock ration. The reverse effect occurred in a dog given a purified diet without liver.

Electrophoretic studies revealed a relative decrease in gamma globulin and increases in the beta-1 and alpha-3 globulin fractions of the plasma in all 3 dogs following repeated removal of whole blood.

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THE DIRECTION OF THE PRECORDIAL T WAVE IN 321 NORMAL INFANTS AND CHILDREN*

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Most of the published reports dealing with the normal precordial electrocardiogram pertain to adults while relatively few studies have been made on normal infants and children. Furthermore, confusion arises in the interpretation of the results since the majority were obtained before the precordial position was standardized by the Heart Associations of America, Great Britain and Ireland.[1,2]

As no study of an adequate number of normal children dealing with the precordial T wave under standardized conditions has been published in the English language, we thought it desirable to make such data available in print. Our series, the largest to date, is concerned with the direction of the precordial T wave of 321 normal infants and children. The question that prompted this study was: "At what age does an inverted T wave in lead CF_4 in normal children become upright?" As the work with these children progressed, other interesting features of the precordial T Wave presented themselves.

A search of the literature revealed that only a few studies dealing with this wave in children have been described. Master, Dack and Jaffe[8] reported on 71 normal children; Robinow, Katz and Bohning[10] on 61 children; Messeloff and Pomerantz[9] on 20 children.

These authors published their reports before the standardization of the precordial position was adopted, so that no exact comparable basis for study may be made. They found the greatest number of inverted T waves when the electrode was near the sternum and in the younger children. In the more recent studies in which the recommended precordial positions were employed, Battro and Mendy[4] reported on 50 children from birth to 10 years old and found inverted or diphasic T waves as far to the left as V_6, during the first 2 years of life, and no inverted T waves in the 6 to 10 years group in positions V_5 and V_6. Goldberger[6] found a downward T in 18% of 50 children from 5 to 11 years old using the V_4 lead. Katz[7] states that "inverted T waves in CF_2 are common in infants and children and may persist into adolescence or occasionally into early adult life. In infants and very young children these may also be present in CF_4." Burch and Winsor[5] in their text write: "The T wave in IV F in the child is often inverted (60% of children in some series). The age at which the T wave becomes upright is unknown." Suarez and Suarez, Jr.[11] found that

* The infants and children that were studied were from the Infants Home of Brooklyn; Colony House Incorporated, Brooklyn; and Public School 27 through the cooperation of the Bureau of Child Hygiene, Department of Health, New York City.

in 40 children, age 5 to 11, there were 38 negative and 2 diphasic T waves in V_1, and conclude that "in children from 5 to 11 years, a negative T wave is probably abnormal only when present in V_6 and perhaps V_5."

Procedure. The subjects for this study were obtained from a nursery home, a public school and a Settlement house. Only those children with hearts thought to be normal were selected. Three limb leads and 5 precordial leads were taken. The precordial positions were those recommended by the Heart Associations of America, Great Britain and Ireland:[1,2] CF_1, CF_2, CF_3, CF_4, and CF_5. The first position is situated at the right margin of the sternum and the second at the left margin of the sternum, both in the fourth interspace. The remaining positions lie on a line extending from the left margin of the sternum at the fourth interspace to the apex, at the level of which, the line is continued around the left side of the chest. The third position lies midway between the left sternal margin and the mid-clavicular line, the fourth position at the mid-clavicular line and the fifth at the left anterior axillary line. The electrocardiograms were taken with the children in the recumbent position.

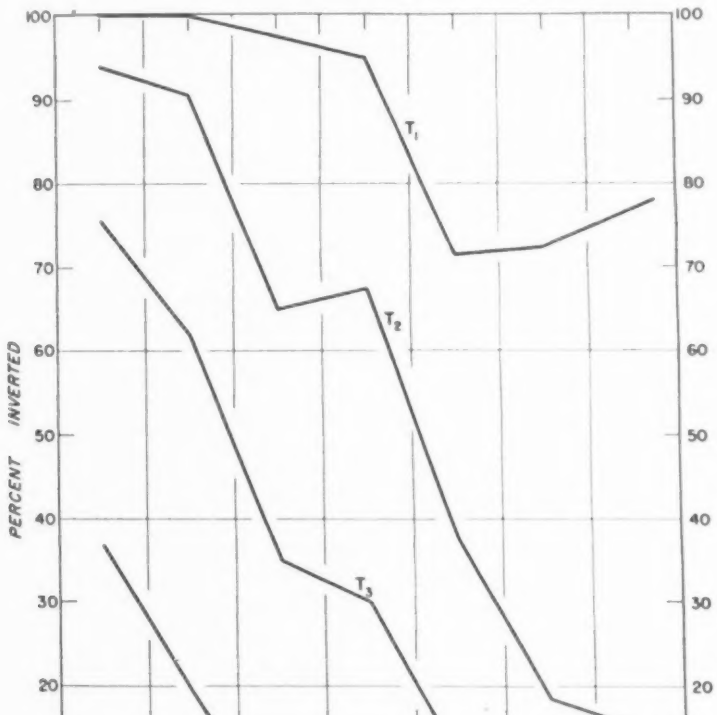

FIG. 1.—Percentage of cases with inverted T waves of various precordial leads.

The over-all results are shown in Figure 1 and Table 1 with the ages of the children recorded at 2 year

intervals, except for the 12 to 14 year group at 3 year intervals. Table 2 itemizes the results at 3 month periods for the first 3 years, and Table 3 at yearly intervals through the age of 14. Diphasic and iso-electric waves are listed as such in Tables 2 and 3; they did not enter into the calculations of percentages of either the negative or positive T waves.

It is seen (Fig. 1) that the highest percentage of inverted precordial T waves was obtained in the youngest children; the smallest percentage of negative T waves was recorded in the oldest children. It is also seen that as the electrode is moved from a position at the right of the sternum across the chest toward the left, from CF_1 to CF_5, there is a decreasing percentage of inverted precordial T waves, at any specified age. The slight rise in the curve for T_1, after 8 years of age is a discrepancy which is probably due to an insufficient number of cases. In other words, for any stated age, the likelihood of obtaining an inverted T wave in a precordial lead is greatest when the electrode is at the right of the sternum and least when at position CF_5.

Lead CF_1 (T_1). There were no upright T waves in 129 children from zero through 6 years of age—Tables 2 and 3. Except for one diphasic T wave in a 5 year old child, all of the T waves were inverted. For the remainder of the 192 children aged 7 to 14, over 70% were inverted.

Lead CF_2 (T_2). Figure 1 and Table 1 indicate over 90% inversions up to 4 years of age. Diphasic and upright waves appeared at younger ages than in the lead to the right of the sternum, CF_1. After age 4 the curve declines rather sharply (Fig. 1) but still shows an appreciable number (14%) of negative T waves in the 12 to 14 year old group.

Lead CF_3 (T_3). This lead follows the same general pattern as the preceding one (CF_2). T is negative in 75.5% of the children in the first two years of life; 35% negative in the 4 to 5 year range, and only 2% of 50 children in the 12 to 14 year group.

TABLE 1.—INVERSION OF T WAVE IN 5 PRECORDIAL LEADS AT VARIOUS AGE LEVELS

Age	No. of Cases	Per cent T_1	T_2	T_3	T_4	T_5
0- 1 Year	49	100.0	93.9	75.5	36.7	6.1
2- 3 Years	21	100.0	90.5	61.9	19.0	0
4- 5 Years	40	97.5	65.0	35.0	2.5	0
6- 7 Years	40	95.0	67.5	30.0	5.0	0
8- 9 Years	56	71.4	37.5	10.7	1.8	0
10-11 Years	65	72.3	18.5	6.2	1.5	0
12-14 Years	50	78.0	14.0	2.0	0	0

Lead CF_4 (T_4). No inverted T waves in the 50 children aged 12 to 14. In this lead only 27 of the 321 children in the total series showed an inverted T wave, while 20 were recorded as diphasic. Positive waves were present in children during the first 3 months of life—Table 2.

Lead CF_5 (T_5). Inverted T waves were found in only 3 of the 49 children (6.1%) aged 0 to 1 years. No negative T waves were present in any child over 2 years of age.

Comments. There is uniform agreement that inversion of T in lead CF_1 is normal in children. This is true for adults as well. On the other hand, the incidence and significance of an up-

right T in this lead has not been as yet definitely established. This problem is posed by Ash[3] who states, "not a sufficient number of analyses of precordial leads from normal infants and children have been reported to enable one to decide at what age the presence of an upright T wave in tracings from the region of the sternum may be considered abnormal. No such waves have been reported for normal children under the age of 12, but the total number of observations has been small." In her series, "upright T waves in the CF_2 lead were obtained from 11 children aged 10 to 14 years inclusive and from 4 children aged 7 to 9 years." Suarez[11] found 22 inverted and 18 diphasic but no upright T waves in lead V_2 in a series of 40 children aged 5 to 11 years, and 2 diphasic and 38 inverted T waves in lead V_1. In our

TABLE 2.—THE T WAVE IN 5 PRECORDIAL LEADS AT 3 MONTH PERIODS FOR THE FIRST 3 YEARS

Age in Months	No. of Cases	T_1			T_2			T_3			T_4			T_5	
		−	D	+	−	D	+	−	D	+	−	D	+	−	D	+
0- 3	6	6	0	0	6	0	0	5	1	0	2	2	2	0	1	5
4- 6	13	13	0	0	13	0	0	11	1	1	6	1	6	1	2	10
7- 9	7	7	0	0	7	0	0	6	0	1	3	0	4	0	0	7
10-12	7	6	0	0	7	0	0	4	1	2	2	3	2	0	1	6
13-15	4	4	0	0	4	0	0	3	0	0	2	0	1	1	0	3
								1 iso			1 iso					
16-18	4	4	0	0	3	1	0	2	0	2	0	0	4	0	0	4
19-21	3	2	0	0	3	0	0	3	0	0	2	0	1	0	0	2
														1 iso		
22-24	5	5	0	0	3	0	2	3	0	2	1	2	2	1	0	4
25-27	6	6	0	0	5	0	1	3	2	1	2	1	3	0	0	6
28-30	2	2	0	0	2	0	0	1	0	1	0	0	2	0	0	0
														2 iso		
31-33	1	1	0	0	1	0	0	1	0	0	0	0	1	0	0	1
34-36	2	2	0	0	1	1	0	1	0	1	0	0	2	0	0	1
														1 iso		

Code: − Negative or inverted; + Positive or upright; D Diphasic; Iso Isoelectric.

TABLE 3.—THE T WAVE IN 5 PRECORDIAL LEADS AT YEARLY INTERVALS FROM 3 THROUGH 14 YEARS OF AGE

Age in Years	Cases	T_1			T_2			T_3			T_4			T_5	
		−	D	+	−	D	+	−	D	+	−	D	+	−	D	+
3	10	10	0	0	10	0	0	7	0	2	2	0	8	0	0	7
								1 iso						1 iso		
4	16	16	0	0	12	2	2	7	2	7	1	2	13	0	0	16
5	24	23	1	0	14	6	4	7	3	14	0	2	22	0	0	24
6	19	19	0	0	15	3	1	8	3	8	1	2	16	0	0	19
7	21	19	0	2	12	4	5	4	6	11	1	1	18	0	0	20
8	27	19	4	4	9	7	11	2	2	23	1	0	25	0	0	25
											1 iso			2 iso		
9	29	21	2	6	12	4	13	4	2	23	0	0	29	0	0	26
10	22	16	2	4	4	4	14	1	3	18	0	1	20	0	0	21
11	43	31	6	5	8	5	29	3	3	36	1	1	41	0	0	41
		1 iso												1 iso		
12	18	13	1	4	1	3	14	0	3	15	0	0	18	0	0	17
13	17	14	2	0	5	2	10	1	3	13	0	1	16	0	1	16
14	15	12	2	1	1	2	12	0	2	13	0	1	14	0	0	14

series, upright T waves in CF_1 were inscribed at age 7 and with increasing frequency thereafter; and in CF_2 at about 2 years of age and with regularity at 4 years of age onward.

It has been our custom, and that of many others, to use precordial leads CF_1 through CF_5 for the electrocardiographic studies of our children. Other clinics routinely use positions CF_2 and CF_4 only. However, the data in this report indicate that for the determination of the direction of the T wave no valuable information is gained by using leads CF_2 and CF^3 that is not more significantly illustrated in leads CF_1, CF_4, and CF_5. This is so because in lead CF_1, no upward T wave appeared in 129 children from birth to 7 years of age—findings not obtained in CF_2 or CF_3. Although the number of children is too small to justify definite conclusions, the presence of an upright T in CF_1, in children 7 years and younger should warrant further study to determine that some cardiac abnormality does not exist. Similar consideration should be paid to lead CF_4 which showed no inverted T wave above 12 years of age. In the report by Suarez and Suarez, Jr.[11] already mentioned, 1 child of a series of 40 children aged 5 to 11 showed a negative T wave in V_5. In the present series no child older than 2 years had a negative T wave in CF_5.

Summary. The direction of the T wave of 5 precordial leads was studied on 321 normal infants and children.

1. The T wave in CF_1 was inverted in 100% of 129 children from zero through 6 years inclusive, except for one diphasic wave in a 5 year old. No upright T was found in these children.

2. The T wave in CF_2 was inverted in 90% of cases up to 4 years of age.

3. The T wave in CF_3 followed the same general pattern as in CF_2.

4. The T wave in CF_4 was inverted in only 27 of the 321 children (8.3%), and in 20 it was diphasic. There was no inversion in 50 children aged 12 through 14.

5. The T wave in CF_5 was inverted in 6% of the cases up to 2 years of age, with no inversions thereafter.

6. It is suggested that leads CF_2 and CF_3 offer no significant information that is not contained in CF_1, CF_4, and CF_5.

We wish to express our appreciation to Miss Marjorie T. Bellows, Statistician of the American Heart Association, for her review of the data and helpful suggestions. We also wish to thank the Electro-Physical Laboratories, New York City, for the use of their direct writing electrocardiograph.

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NATURALLY-OCCURRING ANTICOAGULANTS AND ACCELERATOR SUBSTANCE IN HUMAN BLOOD

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This report is a summary of our experience with naturally occurring hypercoagulable and anticoagulant substances in human blood. The presence of these substances and their effect on the prothrombin and coagulation times in thromboembolic diseases are demonstrated in this article.

Historical Review of Heparin. As far back as 1880 Schmidt-Mülheim[10] made the observation that blood loses its capacity to clot following peptone shock in dogs. The anticoagulant produced by peptone shock in dogs was isolated by Wilander[14] in 1938 and found to be heparin. The source of heparin was thought by Holmgren and Wilander[7] in 1937 to be the granules of the mast cells of Ehrlich. These cells are found around capillaries and small blood vesseis without a muscular coat. Jorpes[8] has found that neoplastic and inflamed tissue rich in capillaries are also rich in mast cells. Brinkhous *et al.*[3] further demonstrated the presence of a heparin co-factor contained in normal human plasma without which heparin is ineffective as an anticoagulant. Holmgren and Wilander[7] discovered that heparin is precipitated by toluidine blue. The anticoagulant effect of heparin is thought to be due to its high molecular weight and its exceptionally strong negative electrical charge. Chargaff and Olson[5] in 1938 demonstrated that heparinized blood can be made to clot by adding protamine which neutralizes the negative electrical charges of heparin.

Following the use of the atomic bomb on Hiroshima a gross bleeding tendency was observed in the victims there subjected to massive irradiation. The mast cells in the tissues of the survivors were shown by the observers to be generally increased. Similarly, an anticoagulant-like substance can be produced by the irradiation (Roentgen-ray) of dogs. The nature of this anticoagulant is apparently heparin since its effect can be temporarily removed by protamine or toluidine blue.[2] Allen[1] has also shown that an increased amount of heparin-like substance may be present in the blood of patients with thrombocytopenia.

Method. The prothrombin technique of Link-Shapiro modification of Quick's method, using rabbit lung as the source of thromboplastin, was used.[4] The thromboplastin used gave an average whole plasma prothrombin time of 12.5 seconds. The 12.5% plasma prothrombin time (made by diluting whole plasma with physiological saline) was 28.5 seconds. The error allowed for whole plasma is 0.5 second and for 12.5% plasma, 1.0 second. A single lot of thromboplastin and chemicals was used throughout this study. The same technician performed all determinations. The three tube method of Lee-White was used to perform the coagulation time. In our hands the normal coagulation time is 6 to 9 minutes.

Observations. 1. ILLUSTRATIONS OF ANTICOAGULANTS AFFECTING SERIAL DILUTIONS OF WHOLE PLASMA PROTHROMBIN. Fig. 1 represents arbitrary dilutions of normal plasma, plasma obtained from a heparinized normal individual, plasma obtained from a dicumarolized normal individual, and plasma obtained from an untreated patient with pulmonary infarction which contained an anticoagulant-like substance (auto-anticoagulant). These dilutions were made by diluting whole plasma with physiological saline solution according to the method outlined by Quick.[9]

The dilution curve of whole plasma prothrombin shown here is a representative one for rabbit lung thromboplastin. The heparinized plasma dilution curve illustrated is from a normal individual whose blood was taken 45 minutes after administration of 50 mg. of heparin intravenously. From this curve it is evident that heparin exerts a maximum effect upon the whole plasma prothrombin time and a slight effect upon the more dilute prothrombin times when compared with the curve of normal plasma. The effect upon the prothrombin time of heparin is immediate and is usually not detectable 4 hours after it is administered parenterally. The action of heparin is also observed in a prolongation of the coagulation time.

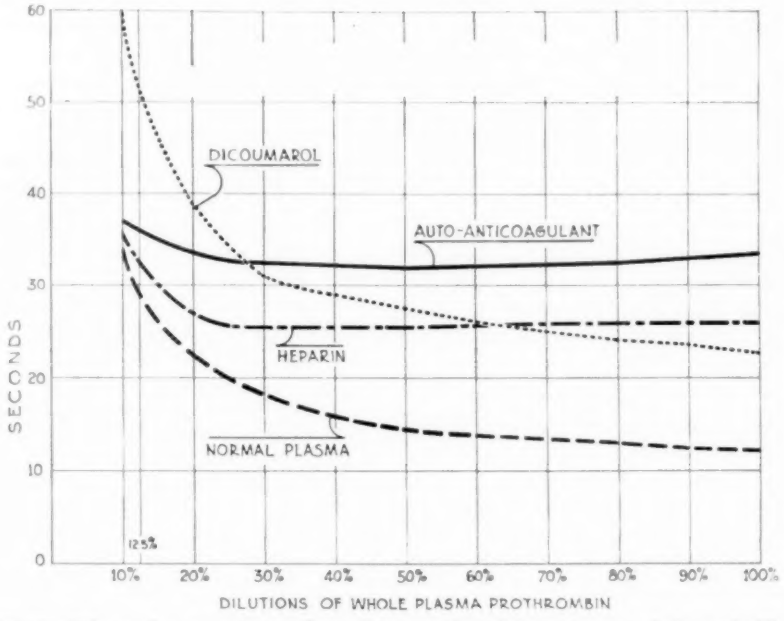

FIG. 1.—Effect of auto-anticoagulant, Dicumarol and heparin on whole and dilute plasma prothrombin.

The dicumarolized plasma represented in Fig. 1 is from a normal individual on daily therapeutic doses (50 to 150 mg.) of Dicumarol. Prolongations in prothrombin times of dicumarolized plasma occur in all dilutions as illustrated in this figure. Dicumarol produces a moderate prolongation of the whole plasma prothrombin time and a marked prolongation of the dilute plasma prothrombin time.

2. Method of Determining Heparin and Dicumarol Dosage During the Initial Phase of Combined Anticoagulant Therapy. After an initial therapeutic dose of Dicumarol (300 mg.) there is an average lag phase of 48 hours before its hypoprothrombinemic effect is obtained. Inasmuch as heparin administered parenterally has an instantaneous effect upon coagulation and whole plasma prothrombin times, therapeutic amounts of heparin and Dicumarol are given simultaneously to obtain an immediate anticoagulant effect. We have found that the 12.5% plasma prothrombin time is the best guide to Dicuramol therapy during the first 48 hours. This is because the 12.5% plasma prothrombin time is only slightly affected by heparin as illustrated in Fig. 1. If Dicumarol is given according to the prolongation of the whole plasma prothrombin time during this period, insufficient dosage will be administered since the prolongation of the whole plasma prothrombin time may be due to the effect of heparin. The obvious method is to take the blood for prothrombin determination at least 4 hours after parenteral heparin administration. However, whether heparin is administered continuously by intravenous drip or in Pitkin's menstruum or intermittently during the lag phase of dicumarol, the prolongation of the 12.5% plasma prothrombin time is the most accurate guide to the hypoprothrombinemic effect to Dicumarol. From our experiences during the combined use of heparin and Dicumarol we have concluded that the whole plasma prothrombin time should be done routinely. However, during this period the 12.5% dilute plasma prothrombin time is the significant determination upon which Dicumarol dosage is based.

3. Diseases in Which Anticoagulant-like Substance (Auto-anticoagulant) Has Been Observed. The effect of the anticoagulant-like substance present in the diseases to be enumerated is detected in the whole plasma prothrombin time but is usually undetectable in the 12.5% plasma since the substance is generally rendered ineffective by diluting 1.8.[11] This effect upon the whole plasma prothrombin time with little or no change in the dilute plasma prothrombin time has been observed in diseases associated with thrombosis, inflammation or necrosis, as shown in Table 1.

TABLE 1.—DISEASES ASSOCIATED WITH ANTICOAGULANT-LIKE SUBSTANCE

Diseases	Number of cases
Myocardial Infarction	70
Phlebothrombosis or Thrombophlebitis	45
Pulmonary Infarction	23
Acute Cholecystitis	4
Carcinomatosis	12
Acute Rheumatoid Arthritis	2
Acute Rheumatic Fever	4
Fractures	9
Cerebro-Vascular Accidents	7
Arterial Emboli and Thrombosis	6

The nature of this anticoagulant-like substance is apparently an inhibiting agent not concerned with the production of prothrombin. The 12.5% plasma prothrombin time can be normal when the whole plasma prothrombin activity is as low as 10%. A normal 12.5% plasma prothrombin time indicates a normal amount of prothrombin present. To cite an example of the extreme quantitative effect of anticoagulant-like (auto-anticoagulant) substance, we recently observed a case of superficial thrombophlebitis of the right leg following trauma to that leg. The patient was a 67 year old female with moderate bilateral saphenous varicosities. She was admitted 2 days following a pulmonary embolus. At this time the patient had a coagulation time of 40 minutes, a whole plasma prothrombin time of 33.5 seconds (normal, 12.5 seconds), and a 12.5% dilute plasma prothrombin time

of 35.7 seconds (normal, 28.5 seconds). On admission the patient was acutely ill and was treated solely with Dicumarol and supportive therapy as only a slight degree of prothrombin deficiency was present. Twenty-four hours later the coagulation time was normal and the inhibitor effect in the prothrombin times was less marked than it was upon admission. At this time heparin was also given until the dilute plasma prothrombin time showed a prolongation to a therapeutic Dicumarol range.

The impressions cited here have been observed during the performance of approximately 9,000 serial prothrombin determinations on a control series of patients.

A dilution curve of plasma containing the anticoagulant-like substance (auto-anticoagulant) closely resembles that of heparinized plasma as illustrated in Fig. 1. Knowing that protamine sulfate possesses the ability to remove heparin from blood *in vivo* and *in vitro*, we have attempted to remove the anticoagulant-like substance (auto-anticoagulant) from the plasma with protamine *(in vivo* and *in vitro)*. In no instance have we been able to eliminate the anticoagulant-like (auto-anticoagulant) effect by protamine sulfate. This leads us to believe the substance observed by us is not heparin. The effect of prolongation of the whole plasma prothrombin time caused by the anticoagulant-like substance has in each instance been observed to disappear following operation, if due to acute surgical inflammatory disease. Similarly, it disappears with subsidence of infection or resolution and fibrosis if from myocardial infarction.

Doles[6] reports the presence of hypoprothrombinemia in acute coronary thrombosis and has treated these patients with vitamin K. He believes the hypoprothrombinemia is an indication of hemorrhage. We too have used vitamin K in the presence of the inhibiting agent but we have not observed any change in the prothrombin time. Indeed, it would have surprised us to obtain a change in the prothrombin determination in the presence of the inhibiting agent, inasmuch as the dilute prothrombin time is essentially normal in its presence and does not indicate a hypoprothrombinemia.

4. Presence of Hypercoagulable and Anticoagulant-like Substance in Myocardial Infarction, Phlebitis and Pulmonary Embolism. In patients with coronary symptoms we have performed serial prothrombin determinations along with the routine work-up for this disease. Several have been observed during the coronary insufficiency stage before a definite myocardial infarction occurred. Most of the prothrombin determinations were normal in both the whole and 12.5% dilute plasmas during this stage. During the observation period 11 patients developed typical myocardial infarctions substantiated clinically and electrocardiographically. At the time of the occlusion these patients have a diminished whole or 12.5% dilute plasma prothrombin time or both (hypercoagulable). The hypercoagulable (accelerator) effect occurs concomitantly with the onset of myocardial infarction. We believe that the prothrombin determination is inadequate in predicting myocardial infarction. An illustration of what occurs to the prothrombin time in myocardial infarction may be seen in Fig. 2. The presence of the anticoagulant-like substance has been observed as early as the first day following myocardial infarction and has usually disappeared by the 3rd to 6th week depending upon the extent of the myocardial infarct as seen in Fig. 2.

The individual with a massive hypercoagulable (accelerator) effect may continue to illustrate this action in the 12.5% plasma during the anticoagulant-

like phase. For example, during the anticoagulant-like phase the 12.5% plasma prothrombin time may be: 1, shorter (accelerated); 2, normal; 3, slightly prolonged or inhibited. This indicates: 1, an increased tendency to clot; 2, a normal prothrombin content; 3, evidence of increased anticoagulant-like substance affecting even the 1:8 dilution.

In difficult diagnostic conditions such as phlebothrombosis and pulmonary infarction, the prothrombin determination of whole and 12.5% plasma is of definite diagnostic value. During the early thrombotic period the times of either whole plasma, dilute plasma, or both determinations will be shorter than normal (accelerator phase). This is followed shortly by a prolonged whole plasma prothrombin time (auto-anticoagulant phase). However, it must be emphasized that these changes may be influenced by certain inflammatory processes already existing.

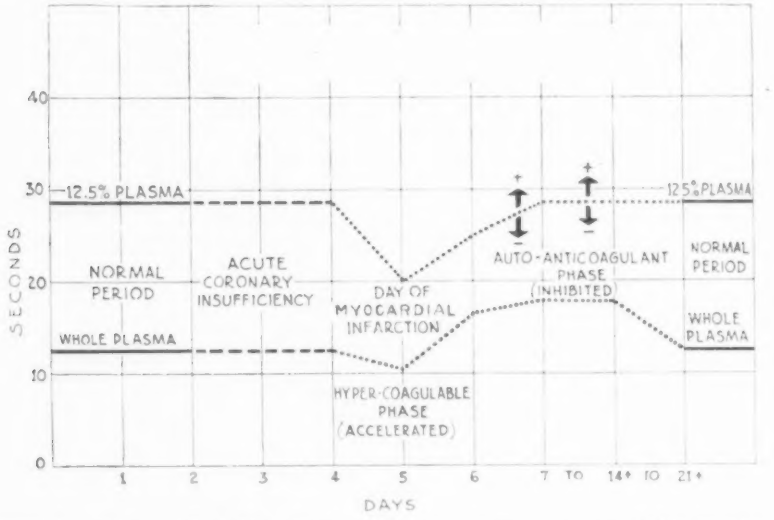

FIG. 2.—Whole and 12.5% dilute prothrombin times in myocardial infarction.

TABLE 2.—EXAMPLES OF PLASMA CONTAINING NATURALLY OCCURRING HYPERCOAGULABLE AND ANTICOAGULANT-LIKE SUBSTANCES

	Whole Plasma Prothrombin Time (seconds)	12.5% Plasma Prothrombin Time (seconds)
1. Normal Plasma	12.5	28.5
2. Hypercoagulable Plasma, Marked Effect	10.0	20.0
3. Anticoagulant-like Plasma, Marked Effect	18.0	34.0
4. Anticoagulant-like Plasma, Moderate Effect	15.0	28.5
5. Anticoagulant-like Plasma, with Hypercoagulable Effect Present	18.0	24.0

Ware *et al.*[12] have demonstrated the presence of an Ac-globulin accelerator factor in normal plasma. With increasing concentration of the Ac-globulin accelerator factor the prothrombin time is made shorter. This plasma Ac-globulin is probably an inert protein or a pro-enzyme.[13] The isolation of this factor clarifies the mechanism of the conversion of prothrombin and fibrinogen to fibrin. Whether this factor is the one responsible for the hypercoagu-

lable plasmas which we have observed is unknown to us.

Discussion. Taking into consideration the presence of a naturally occurring anticoagulant in the above diseases outlined, the fact that thrombosis does not occur in some of these conditions poses the question: Is this Nature's way of preventing thrombosis? In follow-up cases of myocardial infarction, some plasmas have been found to be hypercoagulable. Many of these patients have typical anginal symptoms and others are symptom-free. The question is raised of whether to use prophylactic anticoagulant therapy (Dicumarol) in the presence of hypercoagulability preceding or following myocardial infarction. Hypercoagulable plasmas have been found pre-operatively as well as post-operatively. Some of these patients have a history of phlebitis and others of varicose veins. Whether patients with hypercoagulable plasmas are candidates for phlebothrombosis and pulmonary embolism is a question which needs further investigation. A large series of cases demonstrating this phenomenon will have to be reviewed before a definite conclusion can be drawn.

Summary. 1. A review of the literature on naturally-occurring heparin-like substances is presented.

2. The action of heparin upon the prothrombin time is illustrated and compared with the effect of Dicumarol on the prothrombin mechanism.

3. From the whole and dilute prothrombin determinations there is devised a simple plan for adequate regulation of heparin and Dicumarol during the initial combined anticoagulant treatment of thromboembolic diseases.

4. The presence of naturally-occurring hypercoagulable (accelerator) and anticoagulant-like substances is illustrated with cases cited.

5. The prothrombin mechanism in relation to thromboembolic diseases, particularly myocardial infarction, is investigated and evaluated.

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CONTINUOUS PERITONEAL IRRIGATION IN THE TREATMENT OF INTRACTABLE EDEMA OF CARDIAC ORIGIN*

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The treatment of edema, occurring in the course of chronic congestive heart failure, is in a more satisfactory state today than at any time in the past. By the sufficiently frequent administration of mercurial diuretic agents and, or, a sodium poor diet, together with other rational measures for the treatment of congestive heart failure (rest, digitalis, oxygen), in most instances water retention can be effectively combated. With the patient suffering from congestive heart failure properly trained on a salt poor regime, no longer are the stringent fluid limitations of former years in order. Recent work adequately establishes[6,7] the fact that such fluid limitation is not only unnecessary but distinctly detrimental.

Notwithstanding the general effectiveness of the regime outlined above, an occasional patient is encountered whose edema (or anasarca) responds little or not at all to the measures mentioned. In such patients recourse to other diuretic agents (ammonium chloride, potassium salts, urea, aminophyllin) has been of little value in our experience. Even in instances of established hypoproteinemia, when the strikingly lowered serum albumin seemed to play some part in the genesis of the intractable edema, all clinical measures available to us for the amelioration of the hypoproteinemia proved futile.

The patient in chronic congestive heart failure who responds to mercurial injection with satisfactory diuresis does so, it is believed, because the mercurial acts on the renal tubule, reducing sodium reabsorption. Thus there is a large increase, not only in the total sodium output, but also in the concentration of sodium in the urine.[3]

The patient in heart failure, with extensive water retention, who manifests little or no diuresis after the administration of mercuhydrin or salyrgan, is one in whom such mercurial administration results in little or no additional sodium excretion. Marked reduction in glomerular plasma filtration leads quite obviously to parallel reduction in the amount of salt filtered through the glomerulus into the tubule. This means, as Leiter has indicated,[5] that, as effective as mercury may be in reducing tubular reabsorption (rarely below 96%), in such instance the amount of sodium filtered and failing of reabsorption (and hence excreted) may be insignificant.

Leiter[5] has taken advantage of the necessity of removing ascitic fluid in patients with intractable cardiac edema and ascites by carrying out peritoneal dialysis with the instillation of several liters of 5% glucose. The fluid is removed from the peritoneal cavity after 2 or 3 hours, and is found to contain almost as much salt as the plasma. This

* The author wishes to acknowledge his indebtedness to Dr. S. L. Cohen, who cooperated in the medical management of this case, and to Dr. J. Birnbaum, who performed the necessary surgical measures.

procedure is reported to have the same effect on the individual as an effective dose of mercurial—a profuse diuresis.

We recently encountered a patient with chronic congestive heart failure whose edema was as massive as any we have seen. As detailed below, all the usual measures for securing diuresis proved futile. During 9 days of observation and treatment the fluid retention became progressively more marked. There was no ascites demonstrable on physical examination. Having in mind the technique described by various workers for continuous peritoneal irrigation,[1,2,4,8] we reasoned that considerable sodium loss from the body might be achieved in this case if a suitable fluid were used with such technique. It should be noted that in acute renal insufficiency the irrigating fluid is chemically designed, among other things, to maintain the prevailing state of fluid and electrolyte balance. The objective is solely to provide, in acute reversible renal insufficiency, an extrarenal mechanism for the excretion of nitrogenous and other waste products which, under ordinary circumstances, would be excreted by the kidneys. Our objective, on the other hand, was to use the same technique of continuous peritoneal dialysis, but only for the purpose of ridding the body of considerable sodium (and water). Five per cent glucose was used in this case.

To our knowledge, this is the first case report of a patient with intractable cardiac edema treated by the method of continuous peritoneal irrigation.

Report of Case. Mrs. F. W., 47 years of age, white, married, and nulliparous, was readmitted to the Jewish Memorial Hospital on August 7, 1948. She complained of shortness of breath and marked swelling of the abdomen and all four limbs. She had had several attacks of rheumatic fever in childhood, after which she invariably had dyspnea on mild effort. During the past 10 years this symptom became progressively more marked. Since September, 1947, she took digitalis consistently, and received mercuhydrin injections once weekly. In February, 1948, 7 months before the present admission, she was admitted to the Jewish Memorial Hospital in a critical state with a diagnosis of rheumatic heart disease, mitral stenosis, auricular fibrillation and severe right and left congestive heart failure. Treated by rest in bed, digitalis, very frequent mercurial injections, oxygen, and fluids *ad lib.*, she improved dramatically, and on her discharge, April 1, 1948, after a hospital stay of 37 days, she weighed 67 pounds less than on admission. She was ambulatory at the time.

Following discharge from the hospital, the patient continued on oral digitoxin, 0.2 mg. daily, and received repeated injections of mercuhydrin. How carefully she followed a sodium poor diet is questionable. In spite of marked limitation of physical effort, she became progressively more dyspneic on effort, and finally, orthopneic. At the same time her lower extremities became more and more swollen, and in the several weeks before admission her abdomen and upper extremities likewise became swollen. When her orthopnea finally became intolerable the patient was readmitted to the hospital by ambulance.

The *family history* revealed only that the patient's mother, having suffered from heart disease for many years, died at the age of 50, either of heart failure or a "heart attack".

Physical examination on admission revealed a very seriously ill patient. Blood pressure 130/80. She was markedly cyanotic and orthopneic. There was auricular fibrillation and a heart rate of 90 per minute. Conjunctivae were suffused. Ocular fundi were normal, excepting for marked venous congestion. Facial edema was noticeable. Even in the full sitting position there was marked engorgement of the cervical veins. Coarse moist rales were audible throughout the chest. The heart was markedly enlarged, with the classical signs of mitral stenosis. Rate and rhythm as mentioned. The abdominal wall was so edematous, especially laterally and in the suprapubic region, as to be obviously several inches thicker than normal. The hepatic edge was palpable 3 fingers breadth below the costal margin, firm and not tender. No physical signs of ascites could be elicited. There was massive edema of both lower extremities from the feet through the groins. This edema of the lower extremities was more marked than in any case we can recollect. Both forearms were likewise very edematous, though not gigantically.

Laboratory examination revealed hemoglobin 11.2 gm., erythrocytes 3,400,000; leukocytes and differential count within normal

limits. Blood Wassermann test was negative. Repeated urine examinations revealed specific gravity always between 1010 and 1012. Albumin was consistently 3 plus, and at all times there were numerous hyaline and granular casts. Sedimentation rate within normal limits. Blood chemical examination revealed urea nitrogen varying between 32 and 59 mg. per 100 cc., and blood sugar, serum albumin, serum globulin, cholesterol within normal limits. Standard urea clearance was 17% of normal. Roentgen-ray (portable) examination of chest disclosed marked enlargement of the heart to the right and left, no infiltration or consolidation demonstrable in lung fields. Electrocardiogram disclosed marked right axis deviation and auricular fibrillation with ventricular rate of 90 per minute.

The *diagnosis*, as on the previous admission, was: rheumatic heart disease, mitral stenosis, auricular fibrillation and severe right and left congestive heart failure. In addition, there was renal damage and renal insufficiency with nitrogen retention.

Treatment. The measures which had proven so successful in the management of this patient on the first admission were to no avail. On several occasions mercuhydrin and salyrgan injections were without any effect on the patient's urine output, which remained consistently at 500 to 600 cc. per 24 hours. It was thought unwise to continue mercurial injections under these circumstances. On September 14 the patient was noted to be amaurotic. Neither we nor the ophthalmologic consultant could detect any pertinent fundus or other changes to account for the blindness.

With some misgivings it was finally decided, since the patient was growing worse with greater accumulation of edema, to institute continuous peritoneal irrigation, using 5% glucose with added penicillin. Accordingly, on September 16, 1948, 9 days after the patient's readmission, a No. 24 mushroom catheter and a sump drain were inserted into the peritoneal cavity, the former in the right subcostal region and the latter above the left groin. The connections and apparatus were essentially as described by Seligman, Frank, and Fine,[8] and others.[1,2,4] Penicillin in conventional dosage was administered intramuscularly throughout the period of irrigation. During the interval from September 16 to September 22, 500 to 1000 cc. of 5% glucose per hour were permitted to flow into the peritoneal space. Although improvement was visible, on September 22 the amount was curtailed to 200 cc. per hour because of the poor outflow, and on September 24 both the catheter and sump drain were removed because of scant return. At no time did the patient manifest any symptoms of peritonitis.

On September 20 there was a striking improvement in the appearance of the patient. The facial edema had cleared entirely as had the edema of the forearms. The lower limbs were much less edematous. The edema of the lower extremities continued to diminish rapidly and on September 24, when the catheter and sump drain were removed, there was only minimal pretibial edema. Also on that day the patient was observed to have recovered her vision completely. We have unfortunately, no record of the weight change in this patient, since, when her edema was maximal, our nursing staff found the patient too immobile to get her out of bed for weighing. We are certain, however, that she lost more edema fluid between September 16 (the day the procedure was started) and September 24 (the day it was terminated) than during her previous hospital stay, and on that occasion she lost 67 pounds. The measurements in Table 1 will give some idea of the dramatic decrease in edema.

TABLE 1. COMPARATIVE CIRCUMFERENCES BEFORE AND AFTER PERITONEAL IRRIGATION

	L. calf	R. calf	At level of Iliac crests
Sept. 15	60 cm.	58 cm.	121 cm.
Sept. 25	30 cm.	29 cm.	100 cm.

Serum sodium determination on September 16, before the lavage was started, was 343 mg. per 100 cc. Daily determinations until September 24, the date of discontinuance, disclosed progressive fall in this level to 291 mg. per 100 cc. Total proteins remained unchanged. CO_2 combining power fell progressively from 48.5 to 37.6 vols.%. The drainage fluid at all times contained significant concentrations of sodium, varying from 312 mg. per 100 cc. to 331 mg. per 100 cc.

Comment. This case is reported for the sole purpose of recording the fact that continuous peritoneal irrigation with 5% glucose was followed by striking diminution of edema of cardiac origin in a patient in whom conventional measures had proved futile. Experience in one case of course does not justify a conclusion that this treatment is indicated in all cases of similar character; but it does suggest, we believe, that further study of extrarenal means of depleting body sodium is warranted. Nor are we convinced that

5% glucose is the best possible solution for this purpose. Conceivably a more physiologically acceptable solution can be designed. It is also suggested, if further experience proves the method to be clinically feasible, that it may be applied as well in certain selected cases of non-cardiac edema, if in those instances the continued accumulation of body water threatens the life of the patient. The decrease in body water by the measure described is in accord with the prevailing concept of the role of sodium in cardiac edema. Although no unfavorable results have been observed as a result of the surgical procedure, it is obvious that it should not be employed except in severe cases where non-surgical treatment has been without avail.

Summary. 1. Continuous peritoneal irrigation with 5% glucose was used in a case of congestive heart failure with massive edema in whom conventional measures proved futile.

2. This procedure was followed by great loss of edema fluid and "short term" striking improvement of the patient.

3. The drainage fluid from the peritoneal cavity contained significant concentrations of sodium.

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STUDIES OF A SULFADIAZINE-SULFAMERAZINE COMBINATION WITH SPECIAL REFERENCE TO TREATMENT OF PNEUMONIA*

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Chemical and therapeutic studies of sulfonamide combinations have demonstrated that the total amount of sulfonamide that can be held in solution in urine is substantially increased when two or more of these substances are administered simultaneously.[1,2,5,6] Thus it is possible to diminish the hazard of irritation to the urinary tract from sulfonamide crystals or calculi by means other than administration of alkali. Since sodium bicarbonate or other alkalinizing adjuvants, to be completely effective in lowering the incidence of renal complications, must be given in amounts capable of causing undesirable effects, there is reason to believe that the use of sulfonamides in mixtures is advantageous.

The opinion has been prevalent, particularly among laboratory investigators, that combinations of sulfonamides in mixtures offered no advantage from the purely chemotherapeutic standpoint over the single compounds. Some held that mixtures would be less effective. However, clinical experience, especially that of Lehr,[5,6] suggested that combined sulfonamides were more efficacious. Zeller, Hirsh, Sweet, and Dowling[9] compared the response to sulfadiazine and sulfamerazine, administered simultaneously, to that obtained when the single drug was used in the treatment of meningococcic meningitis. There was a slight, but not significant, difference in case fatality rates with combined drug therapy, but no difference in the clinical course. Toxic reactions occurred with somewhat greater frequency, possibly as a result of the higher daily dosages of the sulfonamides used in combination. Differences observed were minimal and of uncertain significance.

During the past 3 years, sulfonamide mixtures† have been used at this hospital in treatment of pneumonias and other acute systemic infections††. In this paper, the results in treatment of pneumonia have been compared with those obtained by use of sulfadiazine

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† Sulfadiazine-sulfamerazine mixtures used in our studies were supplied as Combisul-DM by Dr. Norman L. Heminway, Schering Corporation, Bloomfield, New Jersey.

†† Clinical facilities were given us for this study by the following Chiefs of Service: Doctors Frieda Baumann, R. S. Boles, C. L. Brown, Thomas Durant, Thomas Klein, D. W. Kramer, D. N. Kremer, W. G. Leaman, Jr., S. A. Loewenberg, and T. G. Schnabel.

alone, from the standpoint of chemotherapeutic effectiveness, toxic manifestations, and the occurrence of crystals of sulfonamide in urine. The latter may be presumed to represent, for the purpose of this comparison, the hazard of mechanical injury to the urinary tract related to low solubility of the sulfonamides used and their derivatives.

Experimental. Two separate therapeutic experiments were conducted. The first employed as subjects the patients with a diagnosis of pneumonia on the Fever Ward of the hospital from February to June, 1946. Since this included only a portion of the pneumonia season, a second series was investigated, starting in December, 1946, and continuing through May, 1947. The plan was that used in previous therapeutic trials by our group, assigning the patients systematically, without selection, to the several treatments that were under comparison. One hundred and sixty-nine patients received a mixture of equal parts of sulfadiazine and sulfamerazine, while 139 received sulfadiazine alone, and 45 sulfamerazine alone. An additional group of 28 patients received the sulfonamide mixture, but, in addition, were given 6 gm. of sodium bicarbonate daily. Patients receiving sulfadiazine or sulfamerazine also received sodium bicarbonate in this amount. Except for the subgroup of 28, none of the patients receiving the drug mixture received alkali adjuvants.

If the patient failed to show evidence of a satisfactory clinical response to sulfonamide medication within 24 to 48 hours after starting therapy, an antibiotic was prescribed as a supplement. Patients who were desperately ill on admission received combined sulfonamide and penicillin therapy and neither these nor the preceding were included in the evaluation of therapeutic response. However, urine specimens from these patients were examined regularly for presence of sulfonamide crystals.

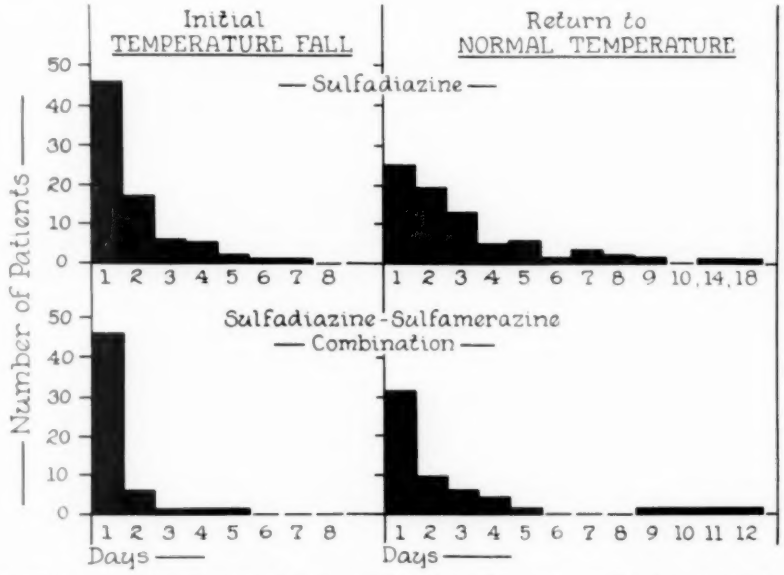

Fig. 1.—The response of patients treated with a sulfadiazine-sulfamerazine combination compared with that to sulfadiazine alone.

The problems arising in connection with the diagnosis of pneumonia have been discussed in a recent paper from this hospital[4] and the reader is referred to it for information concerning the patients undergoing study, as well as the factors influencing the diagnosis. In previous reports, a statement was made that the diagnosis of typical pneumonia was established in every case by the natural history of the disease, the findings on physical examination, and, when indicated, by roentgenological studies. As a result of knowledge gained in recent years, it must now be recognized that by these criteria and by the findings on sputum cultures it is not possible to

differentiate accurately between pneumococcal pneumonias and those of a viral origin. In the present study, pneumococci were isolated from the sputa or blood streams of approximately 70% of the pneumonia patients. Typing was done on pneumococci isolated from blood cultures.

Dosage. Two dosage schedules were employed. An initial 3 gm. by mouth was followed by 1 gm. every 6 hours in all except 22 patients. The latter received an initial dose of 6 gm., followed by 1 gm. every 6 hours. This deviation from the standard dose caused no perceptible improvement in response and was therefore abandoned. The average total dose of the successfully treated patients was about 32 gm. All patients received at least 2500 cc. of fluid during each 24 hour period, insofar as this was possible.

Examination of urine specimens for the presence of crystals of sulfonamide was made as described previously,[1] using the sediment separated by centrifugation from 50 ml. samples of urine. The sediment was suspended in 0.5 ml. of urine and a drop examined under the low power objective of a microscope. The specimens were examined 1 to 2 hours after being voided, being held in the interim in an incubator at 37° C.

Results. The response of the patients receiving the sulfonamide combination was superior to that observed when single sulfonamides were administered. This was manifested by a more rapid initial fall in temperature following administration of the drug and by an earlier return to normal temperature in the groups treated with combined sulfonamides (Fig.1). The differences are sufficiently large to make it unlikely that they are due to chance. Application of the chi square test gives statistically significant P values in both tabulations ($P=<0.02$ and $P=<0.01$) when the number of patients in the 2 groups showing initial temperature fall or normal temperatures respectively is compared. The difference between the mean number of days required for the initial temperature fall is just short of the usually accepted level of significance with $P=0.07$. However, the corresponding difference for return to normal temperature is without significance.

Patients who did not do well on the sulfonamide therapy were given penicillin in addition, and the number receiving penicillin supplementation provides a further test of comparative effectiveness. Eight patients of the sulfadiazine treated (1946-1947) group were so supplemented out of a total of 107 (7.5%), as compared with 6.1% receiving the combined sulfonamides. This is not a significant difference, yet it suggests that the combination therapy was no less effective than sulfadiazine.

The average length of time required for treatment of pneumonia by means of the combined sulfadiazine-sulfamerazine preparation was 6.0 days, as compared with 6.3 days when sulfadiazine alone was used. Patients receiving supplementary penicillin were not included in this comparison. Six deaths occurred in the sulfadiazine treated group and 4 in the combined sulfonamide group, but, only 2 could be attributed to pneumonia, 1 in the sulfadiazine treated group and 1 in the sulfadiazine-sulfamerazine treated group. Each of these patients had received antibiotic therapy in addition to the sulfonamide. The others were the result of complicating disease, including tuberculous meningitis (2), meningococcic meningitis, alcoholism, and hypertensive cardiovascular disease (2), terminal renal disease, and rheumatic heart disease with terminal pulmonary infarct.

Concentrations of sulfonamide in serum. Administration of combined sulfadiazine and sulfamerazine gave an appreciably higher concentration in serum than did sulfadiazine alone. The average concentration during administration of the former was 14.4 mg. per 100 ml. (expressed as sulfadiazine), as compared with 11.3 mg. for sulfadiazine. Sulfamerazine is known to give higher concentrations in plasma than sulfadiazine. This would explain

in part the higher levels resulting from the combined drugs. Another cause is the omission of sodium bicarbonate as an adjuvant. Administration of the large amounts of sodium bicarbonate required to maintain an alkaline reaction in urine depressed the concentrations of sulfonamide in blood.[1] The smaller quantity of sodium bicarbonate used in treatment of some of the patients also had an appreciable effect on plasma concentrations, seen in the group of patients that received sodium bicarbonate (at the rate of 6 gm. daily) with the combined sulfonamides. The average concentration of sulfonamide in plasma was lower by about 10% in this group than in the patients not receiving the alkali.

Crystalluria and urinary tract complications. The use of a combination of sulfadiazine and sulfamerazine resulted in a decrease in the number of urine specimens containing crystals of the sulfonamides (Table 1). The incidence of crystals was higher than that observed initially,[1] but is less than that in the group receiving sulfadiazine or sulfamerazine without alkali. However, the number of patients receiving the combination who showed crystals in urine at some time was about the same as that observed in those receiving sulfadiazine with or without 6 grams of sodium bicarbonate daily. This amount of sodium bicarbonate is less than that found necessary to render the urine sufficiently alkaline to eliminate sulfonamide crystal formation,[1,3] however, we continue to remain in doubt concerning the advisability of giving large amounts of sodium bicarbonate to a group of patients that includes many with impaired cardiac reserve.

In the 1946 series, microscopic hematuria occurred in only 2 of 104 patients receiving combined sulfonamide therapy, as compared with a rate of 5% in sulfadiazine or sulfamerazine treated patients. In the 1946-1947 series, erythrocytes and leukocytes were observed more frequently in urine sediments of the patients receiving the combination (13 of 65 patients) than in those obtained from the sulfadiazine treated controls (4% of the patients). The sediment contained from 2 to 20 erythrocytes per low power field, with more leukocytes than erythrocytes. Since the sediment examined was obtained by centrifugation of 50 ml. of urine, the number of cells present in the urine is small and we believe of minor significance. Furthermore, crystals of sulfona-

TABLE 1.—INCIDENCE OF CRYSTALLURIA IN 4 KINDS OF SULFONAMIDE THERAPY

	Patients			Urine Specimens		
	Total	Number with crystalluria	Per cent	Total	Number with crystals	Per cent
Sulfadiazine-sulfamerazine combination 6 gm. day	169	49	29.0	549	89	16.2
Sulfadiazine 6 gm. day plus 6 gm. sodium bicarbonate	107	24	22.4	306	39	12.7
Sulfadiazine 6 gm./day	32	11	34.6	60	17	28.3
Sulfadiazine 6 gm./day	45	19	42.2	90	25	27.7

mide were detected in association with the cellular elements in only 6 of the 13. Finally, the apparently lower incidence of erythrocytes in the sulfadiazine treated controls is deceptive because the higher average pH of the urine specimens in this group resulting from bicarbonate supplementation would decrease their survival.

Microscopic hematuria of a degree that conformed to the usual clinical use of the term occurred only 3 times in the entire series of 169 patients receiving the sulfadiazine-sulfamerazine combination and 5 times in the 187 sulfadiazine treated patients. Gross hematuria was observed once in the former and once in the latter. The hematuria occurring in the patients receiving the combined drugs was associated with crystalluria only in 1 instance, while the reverse was true in the sulfadiazine treated group.

Five patients of the combination-treated group, in addition to the one with gross hematuria, had toxic reactions which were attributed to the sulfonamides and were considered indications for discontinuation of this therapy: in 1, severe vomiting occurred; another developed a leukopenia of 2800 cells per cu.mm.; 1 showed fever, attributed to the drug; 1 developed an ecchymotic rash, and 1 showed general signs of toxicity. The character and frequency of these toxic reactions did not differ from those encountered in the sulfadiazine treated control group.

Discussion. The present study supports the view that the use of a combination of sulfonamides offers advantages over the use of a single compound.[1,2,4,5,7] The hazard of mechanical injury to the urinary tract is decreased because the total amount of sulfonamide capable of being held in solution is increased when two or more sulfonamides are administered. The therapeutic response, as judged by fall in body temperature, has been demonstrated in this study to be superior when a combination of sulfadiazine and sulfamerazine is administered to that obtained when sulfadiazine alone is used at the same dosage level. Previous studies have shown sulfadiazine and sulfamerazine to be about equally effective, hence the gain is not the result of a superiority of sulfonamide in blood when the combination is used, although the levels obtained were no higher than those obtainable using sulfamerazine alone. The higher concentrations in serum are due to the greater tendency of sulfamerazine to combine with serum protein and also are the result of omission of an alkaline adjuvant. Whether the interesting likelihood exists that the presence of the two sulfonamides increases the effective concentration in fluids within the body, just as it was shown to do in urine, remains to be established.

The low mortality observed with but a single death in each group is, in part, a result of auxiliary penicillin therapy used in pneumonia patients. A factor of selection also enters, in that patients who were gravely ill on admission, were treated at once with sulfonamides and penicillin, although elimination of these patients would have little influence on the comparison that is the subject of this paper. Also, the greater frequency of viral pneumonias in recent years is contributory.[3]

Zeller, Hirsh, Sweet, and Dowling[9] found fever, rash, or conjunctivitis to be more prevalent when a sulfadiazine and sulfamerazine mixture was used in treatment of meningitis, compared with the incidence when sulfadiazine or sulfamerazine alone was used. The incidence of these toxic effects has been low in our series and did not differ from that encountered in the controls receiving sulfadiazine. The dosages used by Zeller and associates[9] were considerably greater than those em-

ployed in the present study and this may provide an explanation for the differences. It should be noted that Zeller and associates attribute all of the increase in toxicity to the use of mixed sulfonamides, without assigning any of the responsibility to the higher dosage and blood concentrations in their mixture treated groups. Objections to their conclusions have been offered by Lehr.[7]

Since the studies described in this paper were completed, trial of combinations containing a third sulfonamide, namely sulfathiazole, sulfamethazine, or others, in addition to sulfadiazine and sulfamerazine, has indicated that the occurrence of crystalluria can be decreased to negligible proportions. The superiority of the triple combinations in this respect suggests that they may eventually replace the double combinations studied in this paper.

Conclusions. 1. The use of a sulfadiazine-sulfamerazine combination, without concomitant alkali therapy, in a series of 169 patients with a diagnosis of pneumonia resulted in a lowered frequency of sulfonamide crystals in urine approaching that observed when sulfadiazine was supplemented with sodium bicarbonate at the rate of 6 gm. daily.

2. The therapeutic efficacy of the sulfonamide combination observed in the treatment of 149 patients was equal to and in some respects was superior to that of sulfadiazine alone in a control group of 107 patients.

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HYPOTENSION

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ALTHOUGH it is not possible to cover every aspect of any one disease in a review of this kind, the purpose of this paper is to present some of the physiologic and clinical advances concerning "low blood pressure" and to correlate these physiologic considerations with clinical symptomatology, related diseases and management. Shock, an abnormal physiologic state associated with hypotension, will not be discussed in this presentation.

Definition. The definition of *hypotension* as employed by various investigators varies according to their respective standards. Studies which indicate an incidence of "hypotension" in normal and healthy people should be viewed cautiously. Blood pressure, like any other biologic phenomenon, has a normal distribution or Gausserian curve. Variations are considerable among a large group of normal people and also from time to time within the same individual. A person who has no symptoms may have extremely "low blood pressure" and still be free from any disease. The problem becomes clinically significant only when disease is suspected because of other manifestations. It is hoped that these various difficulties will become evident as this review progresses.

Thus far in the 53 years since Riva-Rocci applied the rubber cuff to the mercury manometer or since Korotkow demonstrated the advantages of auscultation over palpation, the limits of "normal" blood pressure have not been established. The more common errors of the method which may cause inaccurate, low readings include: (1) failure to exceed the auscultatory gap, (2) too rapid deflation of the cuff, particularly in the presence of bradycardia, (3) leakage of mercury from the apparatus with an initial level below zero, (4) failure to place the apparatus on a surface level with the observer's eye, resulting in parallactic errors, (5) improper placement of the bell over the artery, (6) changes in calibration of the aneroid-type manometers, and lastly (7) improper positioning of the subject's arm[20].

The boundary for the lower level of normal systolic blood pressure has been decreased from 120 to 115 to 110 mm.

of mercury; the last of these is generally accepted, primarily because of precedence. Some have ventured to still lower levels of 100[82] or 90[4]. The United States Army Air Force set 105 as the lower limit of normal prior to 1936[117] but later this was changed to 100[105]. At the same time the Royal Air Force established the lower limit as 110.

The uncertainty of what the lower limit of normal arterial pressure should be is exemplified by Robinson[102], who in 1939 studied 10,833 individuals and established the normal range as 90 to 120/60 to 80; in 1940[101], however, he chose 110 as the arbitrary boundary for the systolic pressure because one-half the previous writers had selected that level. Roberts[100] wrote in 1922 that hypotension was one of the indefinite problems of medicine and that the upper limits of the systolic pressure of hypotension ranged from 100 to 125; he cautiously chose 110 as his dividing line. The most recent textbooks of medicine set the upper limits of hypotension as 110/70. It should be emphasized that regardless of the level of blood pressure, relative hypotension may exist, *i. e.*, the reading may be definitely below the usual one for that individual, even though it may be considerably above "normal" levels[96,100].

Incidence. Early statistical studies of blood pressure revealed that 3.5% of persons in good health had "hypotension" according to the definitions of Alvarez[5] and Barach[8]. In 1939 a study of an urban population indicated that 25% of 11,000 people had systolic levels below 110 and 34% had diastolic pressures below 70. Only 4.5% of the men and 1.7% of the women had systolic pressures under 90, and only 2 men and 4 women examined had systolic pressures below 80 mm. of mercury[102]. A study of bank clerks and other sedentary workers showed that 38% of the men and 58% of the women, whose ages ranged from 17 to 30 years, had hypotension[99]. Johnson[66], selecting 110 and 140 as the limits of normal, reported that only 32% of his patients had normal blood pressure; in 31% the pressures were too high and in 37% too low.

Robinson[102] suggested that statistics on blood pressure released by insurance companies were not valid because of a tendency for physicians to "round out" a figure within the acceptable level for any particular year. As soon as the lower level of 100 was accepted by the insurance companies, the frequency of lower readings increased, and later when 90 was acceptable, the incidence of still lower readings increased. Few physicians would deny an individual insurance on the basis of a deviation of about 5 mm. of mercury in a routine examination. This same statistical lowering of levels for blood pressure appeared in the records of young men examined for duty in the Air Force[55,105]. Although no recent statistical review of insurance records has been made, it is likely that the concept of average normal blood pressure has decreased considerably and that the generally accepted boundary of hypotension must be dropped to remain below the rapidly changing "limits of normal." The most recent available survey of the blood pressures of a large number of people is a report in 1947 based on the records of 43,800 men and 31,458 women, mostly young university students in the United States[14]. Of the men 2.36% and of the women 15.98% had systolic pressures below 100, and 11.69% of the men and 30.22% of the women had pressures between 100 and 109. Previous definitions of hypotension as a systolic pressure below 110 would include about one-half of the women and one-seventh of the men of this series.

The incidence cited above prevails in the United States and Great Britain, but levels considered hypotensive in

these countries might well be "normal" for natives of many other geographic locations. No statistical data are available on the incidence of relative hypotension.

Mechanisms. The actual fundamental factors concerned with reduction in blood pressure are: (1) decrease in circulating blood volume, (2) decrease in peripheral resistance, (3) decrease in cardiac output, (4) increase in size of the vascular bed or (5) decrease in viscosity of the blood. Although each of these factors may be controlled by other variables, there is considerable interdependency among them. In any individual one factor may be of primary importance. Specific initiating factors are numerous, as indicated below. One or more of the above 5 fundamental phenomena are concerned with a decline in blood pressure in either health or disease whether or not the level decreases acutely or is persistently low.

General Physiologic Factors. Some general factors which have been thought to influence the blood pressure of man affect the physiologic mechanism in a general manner. Their action is not clear but deserves mention.

Geographic influences. Whereas the actual cartographic habitat of a person has little to do with his blood pressure, his way of life, diet and physical and emotional customs may have great influence. It has been shown that the average blood pressure of some peoples is much lower than that of others[69]. Although Eskimos have about the same levels of blood pressure as Americans in the United States[40] and lower blood pressures are found in people living in India[83], Central America[67,68,114], West Indies[7,103], China[19,71,131], along the Euphrates[63], or in the Australian desert[91], this cannot be attributed to climate according to Lemann[76]. However, others[10,45,103,115,124] contend that climate does play a part in maintaining lower blood pressure.

Sociologic explanations for variations in blood pressure have been proposed. Kean[67] pointed out that whereas Negroes in Africa have relative hypotension, Negroes in the United States, particularly in the South, have hypertension. Likewise, the West Indians in Panama have higher levels of blood pressure than native Panamanians, among whom there was a greater incidence of hypotension. The environmental strain inevitably imposed upon a "foreign" minority appears to produce elevated blood pressure. In contrast, it has been suggested that the completely communistic form of life of the Australian aboriginal[91] and the low tone of physical, mental and nervous activity of the Arab[63] relieve them from the strain of civilization and spare their cardiovascular systems the burden of associated competition and resultant tension.

Environmental Temperature. Studies on the effect of increased environmental temperature upon blood pressure indicate that temperature and humidity associated with seasonal variations have little influence on blood pressure[47,76]. Experiments with ultraviolet irradiation produced no change in blood pressure. Gottlieb[51] detected no change with more rapid but mild elevations in environmental temperature. Studies of circulatory changes at high temperatures disclosed that though diastolic pressure may fall, there is an early rise in systolic pressure with increased pulse rate accompanying capillary dilatation. The peripheral blood vessels continue to dilate, decreasing resistance with pooling and reducing the return of blood to the heart. Eventually, despite the compensatory tachycardia, return of blood to the heart becomes inadequate and circulatory failure or shock is complete[2].

Heredity. Some workers have speculated that hypotension might be an inherited characteristic[45,128]. Garvin's[49] report of 6 cases of hypotension in one family supports this idea; but without an understanding of the influence of environment, temperament, diet, and other factors, this observation cannot be accepted as proof.

Exercise. As early as 1895[61] the effects of exercise on blood pressure were studied. In 1922 Schneider[110] and Addis[1] reported separate studies indicating that blood pressure increases with exercise, whereas Gambill[48] in 1944 reported that exercise of an extremity reduced diastolic pressure but had little effect on systolic pressure. This he attributed to local release of vasodilating substances. Thacker[128] in 1940 discovered an increase in blood pressure after exercise in normal, hypertensive and hypotensive individuals. In the 2 abnormal groups there was slower response and slower return to normal. He concluded that vasomotor response from other factors plays a more important role in increasing systolic pressure than does pulse rate and that the same factors which govern the emotional status of the individual are influential in the rise in systolic pressure accompanying exercise. When the mechanisms which govern vasomotor response fail, then postexertional hypotension, possibly orthostatic in nature, will manifest itself[33]. There appears to be pooling of blood in an extremity, since maneuvers designed to move blood out of that part prevent the hypotensive reaction.

Fatigue and Sleep. When severe exertion results in fatigue, a fall in diastolic and systolic pressures ensues[85]. After prolonged rest these return to the previous levels. Depressed physiologic function of the endocrinologic and nervous systems as well as a generalized decrease in muscular tone are believed to be the mechanisms responsible for the decline. The latter is said to account for the reduction during sleep[10,45,85] and hypnosis[41]. Tone has been defined by Dorland[28] as "the condition of tension of normal muscles which exists independently of voluntary innervation."

Fever and Inflammation. Blood pressure may rise or fall during development of fever[3]. Often no change is noted during prodromal states[112] but occasionally there is a rise during a chill due to vasoconstriction. Since the level of blood pressure is a reflection of the state of constriction of the blood vessels on one hand and of a variable decrease in cardiac output on the other, if the latter is great, hypotension develops despite vasoconstriction. During the flush phase of vasodilatation blood pressure drops.

The strain placed upon the vasomotor regulatory mechanism in prolonged or repeated febrile episodes may account in part for the commonly encountered postinfectious state characterized by vasomotor or cardiomotor instability, hypotonus and concomitant lowering of blood pressure[3]. Taylor and Page[126] discredit fever and leukocytosis as a cause for a diminished blood pressure following nonspecific inflammatory processes. They suggest that inflammatory reactions impair function of the adrenals, which in turn may effect a reduction in blood pressure.

Nutrition. Dietary management of high blood pressure is now popular. The mechanism of the rice diet has not yet been established, although a reduction in protein[70] or sodium metabolism[53,111] is thought to be an important factor. If Nye[91] had advocated the dietary habits of the Australian aboriginal as a means of lowering blood pressures, then hypertensive Americans would today be gorging themselves with game meat for several consecutive days and then abstaining

from food for several more. He suggests that the products of protein metabolism may possibly be completely eliminated during the periods of fasting. Also there is little salt in the food of these people as well as in the fruit diet of the Cuna Indians of Panama[68]. Shattuck[114] suggested that the low blood pressure of the Guatamalan was possibly due to a deficient diet.

That starvation diets and diets inadequate in protein depress blood pressure is further supported by reports of observations on starving Europeans and prisoners of war[77,78] and of planned experiments on volunteers at the University of Minnesota[125]. The increasing incidence of tuberculosis and other diseases among the starving Europeans may have played a role in the decline in the average levels of blood pressure. Psychic or emotional factors cannot be completely excluded in these studies. During the period of anxiety prior to starvation, levels of blood pressure were highest; when the starvation period was in effect and hostile occupation forces were suppressing the peoples so that all hope was abandoned, hypotension became most prominent. With renewal of hope and resumption of the problems of competitive living, the average blood pressure became elevated again.

Other cachectic states, such as anorexia nervosa or Simmond's disease, are associated with hypotensive pressures which are not as extreme as those seen in Addison's disease. It is difficult to separate the influence of the generalized psychic depression from that of depression of endocrinologic systems. Regardless of the initiating factor, severe undernutrition in rats results in a physiologic pattern resembling that of the hypophysectomized animal[90]. The caloric deprivation and reversible pituitary depression in man is accompanied by decreased adrenal cortical activity[123]. This is also true of the other endocrine glands which are concerned with maintenance of fluid and electrolyte balance, blood pressure, vasomotor stability and muscular tone.

The role played by vitamin deficiency is unsettled but in the cardiac type of beriberi, the blood pressure may be normal or low[119]. Rats with vitamin E deficiency have been shown to have blood pressures 29% lower than nondeficient controls[127].

Specific Physiologic Phenomena. There are physiologic phenomena which are more specific in their role in the regulation of blood pressure than those just described. Some of the more important ones are presented.

Reflex phenomena. Certain reflex phenomena are concerned with regulation of arterial blood pressure. Although they are probably related to some extent to all forms of hypotension and all specific mechanisms, some aspects of their role deserve separate consideration. Heymans[60] and Bronk[17] discuss in detail the pressoreceptive mechanisms which regulate cardiac rate, vasomotor tone, and blood pressure. Pressosensitive areas are situated in the carotid sinus and the venoauricular, pulmoarterial and thoracosplanchnic areas. They are reflexogenic and react to changes in intravascular pressure so that when the pressure increases, reflex vasodilatation and cardiac slowing occur with diminution in cardiac output. The reverse occurs with a decrease in intravascular pressure in these areas. In many other vascular areas local vasomotor reactions take place. The normal organism is able to compensate for sudden transient changes in blood pressure invoked by a disturbance in one of the fundamental factors, but if the reflex proprioceptive regulators become depressed or paralyzed, then compensatory power is lost. Some of the causes may be acute, such as trauma to the areas, severe anoxemia, including that pro-

duced by hemorrhage, spinal anesthesia, deep general anesthesia, administration of barbiturates, morphine or other narcotics, hypocalcemia produced by injection of citrate or oxalate or parathyroidectomy, pulmonary hyperventilation, histamine, ergotamine or the dioxane-like substances. With the regulating mechanism depressed, permanent fall in pressure results from some initiating stimulus, and circulatory collapse follows.

More subtle depression of the regulatory centers which protect against extreme variations of blood pressure may permit persistently lower or higher levels, depending on the nature of the stimulus. These physiologic phenomena are made more complex by the relation between the mechanisms regulating blood pressure and those adapting the peripheral circulation to nutritional needs of the tissues and organs. Vessels dilated to meet local metabolic demand do not undergo nervous or adrenic vasoconstriction.

It should be pointed out that suprarenal and neurovascular reflex regulators of the blood pressure may act independently. The zone of the carotid sinus, when the carotid body is included, is chemosensitive as well as pressosensitive, so that changes in oxygen or carbon dioxide or the presence of one of several drugs in the blood can influence the centers and modify the blood pressure[60].

Although the arteries of the central nervous system are not thought to participate actively in the general reflexive regulation of blood pressure, the cerebral blood supply is constantly dependent upon the general systolic arterial pressure, which is regulated by the aorta and carotid sinus[13]. In cases of decreased systolic arterial pressure, peripheral and splanchnic vasoconstriction deviate blood into the cerebral circulation.

Reflex syncope may follow the occurrence of transient hypotension in persons with a hyperactive carotid sinus reflex[37,46,116,134,135,137]. Three types of carotid sinus syndromes are described: (1) cardiac inhibition, (2) vasodepression, in which a sharp drop in blood pressure may occur without cardiac inhibition and, (3) the cerebral type, with no fall in blood pressure. The fall in blood pressure usually occurs at the time of syncope, and as a rule bradycardia is present. These physiologic reactions do not occur if the carotid area is denervated[137]. Anatomic enlargement of the carotid sinus has been reported in the hypersensitive individual[37,137]. Syncope has been attributed to cerebral anoxemia produced by asystole and fall in arterial blood pressure[46].

Vasodepressive syncope is seen in conditions other than the hyperactive carotid syndrome. Stimulation of the arterial wall, not associated with pain and not related to psychic factors, has been shown to produce peripheral vasodilatation, tachycardia, considerable fall in blood pressure and collapse in one-third of the individuals tested in this manner[108]. Syncope associated with venipuncture and accompanied by reduced blood pressure is often encountered in blood donors and has been attributed to psychic influences[89]. In reporting syncope and fall in blood pressure accompanying exertional dyspnea and angina pectoris, Golden[50] suggested that the heart was unable to increase the cardiac output during exertion or to increase its output in response to reflexes arising from engorged lungs or an ischemic myocardium.

It has been suggested that stimulation of the arch of the aorta might be a factor[12] in the hypotension occurring during thoracic surgical operations. It was concluded, however, that alteration of blood pressure was due to mechanical impediment of blood flow to the

heart by compression of vessels. Because this would also increase intravascular pressure, the presence of a reflexogenic pulmoarterial area was suggested which might be concerned with the hypotension.

Local increases in pressure are thought to play a large part in the lowering of systemic pressure in pulmonary arterial occlusion[55]. The extreme constriction of the entire pulmonary vascular bed, which impairs the pulmonary flow of blood, diminishes the output of the left ventricle, producing a decline in arterial blood pressure. Atropine and papaverine have been said to relieve this vasoconstriction dramatically and to permit restoration of the cardiac output[27].

Penetrating wounds of the chest[86] may reduce the blood pressure by afferent impulses arising in the pleura which produce arteriolar dilatation.

Postural maladaptation. The relationship of posture to blood pressure was studied as early as 1895[61], but it was not until 1925, when Bradbury and Eggleston[15] reported their cases of postural hypotension, that it was regarded as a disease entity. The physiologic adaptations concerned with adoption of the erect posture and relation to gravity has since received much study. Factors operating to maintain blood pressure in the erect posture are discussed in recent reviews[92,120]; they are essentially (1) peripheral vasoconstrictions, (2) acceleration of the cardiac rate, and (3) greater tonus of skeletal musculature. The compensatory mechanisms are not simple and not agreed upon generally.

There has been lack of agreement as to the mechanism for the reduction in pressure. Ellis and Haynes[34] suggested that it was due to greater than normal pooling of blood in the lower extremity. MacLean, Allen and Magath[80], by use of the Flack test, asserted that failure of adequate return of venous blood to the heart is an essential factor in the syndrome of orthostatic hypotension. This test consists in increasing intrathoracic pressure of the subject by forced exhalation against a column of mercury and measuring the length of time the pressure can be maintained. Experiments employing tourniquets and tilting in normal subjects and in persons with postural maladaptation indicated that there was no more pooling in the lower part of the body in a maladapted individual on standing than in a normal individual but that the reflex vasoconstriction which maintained the pressure in a normal individual did not occur in these patients. This lack of adequate reflex vasoconstriction in the face of a decline in pressure is a fundamental disturbance in postural hypotension and suggests that it is a disorder of the sympathetic nervous system[122]. Absence of sweating, loss of libido, and other clinical manifestations of the syndrome tend to support this concept. These findings are not necessarily incompatible with the concept of reduced venous return, since the defective vasoconstriction probably gives rise to diminished venous return[92].

From a study employing tagged erythrocytes Nylin[92] concluded that circulation is abnormally slow in the erect posture in postural maladaptation. This was indicated by the fact that even distribution of the tagged cells required more time in patients with postural hypotension than in normal subjects. Kvale[74] also showed that there was a larger increase in the arm-to-tongue circulation or arm-to-foot time in subjects with orthostatic hypotension following sympathectomy.

There are differences of opinion concerning the cardiac rate in postural hypotension. Some observers[15,16,31,43,122] have reported no change, whereas another[56] found an increase in the rate. Obviously, therefore, there may or may

not be a change in cardiac rate depending upon the activity of the cardioaccelerator reflex mechanism[65]. Functional disorders with associated postural hypotension in particular are apt to be accompanied by "orthostatic tachycardia"[54,75,80,81]. The electrocardiogram has not been found to be abnormal[56,92].

Although the clinical conditions with associated postural maladaptation may be numerous, investigators agree that lesions of the sympathetic nervous system[15,31,122,144], probably in the region of the hypothalamus[11,92], are most often the initiating cause. This obviously does not include cases associated with local lesions of the sympathetic nervous system or patients who have had sympathectomies[26,56,65,106]. In the latter hypotension is usually relative and not absolute.

Biochemical influences. Anderson and his associates[6] induced fainting and lowering of blood pressure by administration of 7 to 8% oxygen, which produced active vasodilatation in the skeletal muscle and a decrease in cardiac rate. On the other hand, hyperventilation with excessive loss of carbon dioxide will cause lowering of the blood pressure in animals[121]. This is true for man as well[64,118]. It has recently been demonstrated that administration of carbon dioxide will prevent the "blackout" associated with centrifugal forces. This action is presumably through increased activity of the carotid sinus and resultant increase in muscular tone and decrease in the quantity of venous pooling[132].

The exact role of electrolytes in maintenance of blood pressure remains unknown. It is probably related to the endocrinologic system. There is decreased concentration of blood chlorides caused by the increase in urinary excretion in pulmonary disease, for example, pneumonia, tuberculosis and carcinoma of the lung[141]. Adrenal dysfunction may be present in these diseases, though no consistent abnormal pathologic finding has been described. The sodium content of the serum does not vary as greatly as the chlorides, the differences being accounted for by compensatory changes in bicarbonate. Low sodium and chloride content of serum observed as a result of the treatment of congestive heart failure and chronic renal disease with depletion of salt[130] are frequently accompanied by shock-like states[97].

Psychic factors. Influence of the psyche on the cardiovascular system is difficult to evaluate and is for the most part still a matter of impression. Engle[36] and Romano[104] attempted to differentiate between vasodepressor and hysterical fainting by use of the electroencephalograph. Kremer[73], who stimulated the cortex by acetyl-beta-methylcholine or faradic current, was able to localize areas which would produce lowering of blood pressure in dogs. The relationship of organic lesions of the nervous system to regulation of blood pressure has been indicated.

Most observers agree that functional disorders are related to the development of hypotension. The strenuous daily activities of civilization serve as stimuli which tend to maintain an increased "tone" of the physiologic systems. When people lack these stimuli or become psychically disturbed so that the pressure of the physiologic systems fails to be properly influenced by the conscious and subconscious levels, the blood pressure declines below the *average* for the "civilized" world or for the psychically normal person but it is not necessarily below *normal*. In severe depressive states the "tone" of the system is decreased and "hypotension" becomes manifest.

Drugs. The vasodilating effect of the nitrite group of drugs, with subsequent lowering of the blood pressure, is well known, the mechanism dealing pri-

marily with peripheral vascular dilatation[138,140]. Similar effects noted with acetylcholine and nitroglycerin are not completely inhibited by adrenal demedullation or cardiac denervation[58].

Hypotension has been said to be produced by histamine or histamine-like substances, an idea particularly prevalent today because of increased interest in antihistamine drugs[44,45]. Carnosine, related to histidine and of unknown metabolic significance, present in mammalian muscle, has been shown to have severe depressive action on the blood pressure[139].

Many agents used in therapy will induce a transient decrease in blood pressure. Some, such as plasmochin, act upon the central nervous system to depress sympathetic activity and produce hypotension[88]. Pentaquine (SN-13276), another antimalarial drug, will produce postural hypotension which may last for months[25]. Page[94] reported a case of poisoning with arsenic trioxide in which there was a mean pressure of 30 mm. of mercury with no ill effects. Other drugs which have been reported to reduce the blood pressure are cinchophen, bismuth subnitrate, and intravenous quinidine[45]. Connell[21] showed that there was no relation between blood pressure and the levels of thiocyanate naturally occurring in the blood.

Interrelationship of all physiologic factors. In summarizing factors related to internal and external environment which alter or maintain blood pressure, we must remember that social surroundings of an individual influence his emotional state, that his reactions will depend upon early training and possibly on heredity, that starvation cannot be considered separate from depression of the psyche or of the endocrinologic systems, that diet and electrolytic metabolism and their relation to endocrinologic or nervous functions influencing the cardiovascular systems are inseparable. We may say, therefore, that inanition, whether due to starvation or to illness, probably exerts a depressing influence on bodily "tonus," endocrinologic function, and reactivity of reflexogenic centers; psychic disturbances manifest themselves by depressing general bodily reactions and tone or by stimulating or depressing certain reflex centers; deprivation of electrolytes (sodium and chloride) perhaps has its influence on blood volume or on the adrenal cortical regulators; and special cardiovascular governors manifest themselves in loss of constrictor power, cardiac inhibition, or failure of cardiac compensatory mechanism. We may also conclude that there is an undetermined interrelation among these factors which ultimately display failure of one or more of the physical mechanisms for maintaining blood pressure, namely: (1) blood volume, (2) peripheral resistance, (3) cardiac output, (4) size of the vascular bed and (5) viscosity of the blood.

Influence of hypotension on certain organic systems. When the mechanisms which tend to maintain adequate flow of blood to the brain are fatigued or dysfunctioning or when there is sudden fall in blood pressure, anoxia of the higher centers ensues. Though the effects of hypotension on mental and physical efficiency have not been established by objective methods, impairment of cerebral function was suggested in a study of fatal air crashes, considered to be the result of errors of the pilots. Seventy-three % of these pilots exhibited some form of hypotension[143].

In spite of coronary vasodilatation with decreased resistance, hypotension is associated with decreased coronary flow[93]. Circulatory collapse, often associated with severe hypotension, may persist despite return of coronary flow to normal. Eckenhoff[32] reported that he observed in dogs a decline in blood

pressure accompanied by decreased cardiac efficiency although there was no evidence that the heart was less able to accomplish the work demanded of it. Left ventricular work was reduced 56% and cardiac output 42%, with 29% decrease in coronary flow. These experiments failed to reveal that certain types of hypotension are harmful to the heart.

With a decrease in cardiac output or fall in arterial pressure, the rate of renal plasma flow is lessened; but the exact mechanism for the decline is still unsettled. Investigators believe that the flow through the kidney is diminished because of the decrease in pressure head and the other physiologic phenomena associated with some of the hypotensive states, for example, increase in viscosity of the blood, pooling of blood in the venous system, liberation of humoral vasoconstricting substances which produce afferent arteriolar constriction of the glomerular tufts[23,24]. When there is extreme diminution of blood flow to the kidney accompanying severe hypotension, urinary output ceases. In subjects with postural hypotension decreased urinary flow during the day is followed by compensatory nocturia.

Pepper[96] is of the opinion that the onset of hypotension, absolute or relative, predisposes to formation of arterial thrombi, particularly in people with arteriosclerotic disease and roughened arteries which impair blood flow. The increase in viscosity of the blood associated with the hemoconcentration often encountered in hypotensive conditions[18] also predisposes to impairment of flow and formation of thrombi.

General health is not unfavorably affected by hypotension[30,55,82,100]; in fact life expectancy has been found greater in the presence of low blood pressure[44,62]. Hypotension seems to preserve rather than injure the physiologic system. After the age of 50, things being otherwise equal, hypotension may be interpreted as a sign of an efficient and healthy cardiovascular renal system[85].

Clinical Picture. The clinical picture associated with hypotension varies with the rapidity and degree of reduction in blood pressure. A sudden fall, regardless of previous levels, is manifested by symptoms of giddiness, faintness, and loss of consciousness, all of which may be attributable to cerebral anoxia.

However, if chronic, sustained hypotension is associated with symptoms, the clinical picture is different. It should then be understood that hypotension itself is but one manifestation of the primary disorder which is responsible for the multitude of associated symptoms, such as generalized weakness, fatigue, dizziness, fainting, gastro-intestinal complaints, belching, flatulence, palpitation, insomnia, numbness in the extremities and many others. It is apparent that such nonspecific symptoms will be encountered in hypertensive and normotensive subjects as well. Anhidrosis, impotence, and nocturia are additional manifestations of postural hypotension.

As is true of symptoms, observations made on physical examination and laboratory data are dependent upon the primary disorder. In asymptomatic essential hypotension there will probably be no constant associated signs. These individuals are likely to be well adjusted and well developed and to have no abnormal physical findings. A particular physical type has come to be associated with hypotension occurring simultaneously with other symptoms. Although obesity, not to be confused with hypersthenia[10], may be accompanied by low blood pressure, the hypotensive individuals fall into the linearly built, underweight class about twice as often as in the laterally built, overweight group[30,101]. The habitus and

accompanying signs should not condemn a patient categorically as a constitutionally inadequate individual.

The body temperature of many patients of both the asthenic group[98] and the essential hypotensive class is lower than that of other individuals. In hypotension the pulse is variable. Of diagnostic value is the finding that in postural hypotension with absence of sweating the skin is dry, whereas in the neurasthenic patient it is moist. Hypotensive individuals frequently have narrow nostrils and nasal obstruction, decreased thoracic capacity, and often signs of asthma[8,10]. Manifestations of enteroptosis are usually found even in the presence of obesity.

Frequently associated with postural and essential hypotension are anemia, low basal metabolic rate, reduced gastric acidity[72], low blood sugar[9], low blood chloride[10,141], and blood urea nitrogen at the upper limit of normal or slightly elevated[99]. Roentgenographic examination of the asthenic hypotensive subject reveals the arch of the aorta to be small, the heart to be vertically placed and together with the great vessels to appear elongated[10,42]. There are no significant electrocardiographic abnormalities.

Clinical Conditions Associated With Hypotension. The conditions provoking or associated with hypotensive levels of blood pressure are legion. Some of these will be listed and a few of the most important will be discussed. For the sake of organization, a modification of Stieglitz's[124] clinical classification will be used.

Acute fall in blood pressure occurs in shock, medical or surgical; food poisoning; fright; during or after administration of anesthetics, vasodilating drugs or poisons; anaphylactic reactions[44] and pulmonary embolism[27,55].

Subacute hypotension is associated chiefly with infectious diseases. Typhoid, scarlet fever, typhus, influenza, malaria, trichinosis, pneumonia, and cholera[8,10,44,45,99] all produce hypotension as a result of dehydration, fever, electrolytic imbalance, lowering of bodily tonus and some degree of myocardial weakness. In pneumonia early severe fall in blood pressure is of serious prognostic significance, comparable to absence of leukocytosis in this disease[10]. There may be prolonged hypotension following convalescence. Renal disease[130] in some stages, when accompanied by loss of electrolytes, diabetic acidosis, or peptic ulcer[96], may also provoke lowering of blood pressure. The initial fall seen after myocardial infarction has been ascribed to peripheral circulatory collapse of reflex origin and to forward failure consequent to left ventricular infarction[87]. Persistent low pressures for 3 to 5 days indicate a poor prognosis. Most surviving patients with previous hypertension have a return of blood pressure to hypertensive levels after one year[44,87,95].

Chronic hypotension, besides being an integral part of the hypotonic, hyporeactive state[72], is associated with the chronic endocrinopathies, anemia, and chronic infectious diseases. It is one of the diagnostic criteria for Addison's disease[55,129] and is a common accompaniment of Simmond's disease and hypothyroidism[41,99]. Hypopiesia may exist with certain constitutional states involving a decrease in muscular or vascular tone, such as myasthenia gravis, status lymphaticus[10,99] and myotonia atrophica[38]. The systolic pressure may be as low as 60 to 80 mm. of mercury in pernicious anemia[10,41,99].

Chronic focal infections and toxemias are frequently accompanied by hypotension[10,41,45,99]. Decrease in the tone of the skeletal, smooth and myocardial muscles and toxic depression of the endocrine glands and of the sympathetic control of the vascular tone are suggested mechanisms. The possible influences of toxic products, such as sub-

stances like histamine[44,99] or carnosine[139], must be considered.

Association of hypotension with tuberculosis has been reported since the early days of the mercury manometer. In 1911, Emerson[35] presented a comprehensive review of this subject, stressing the diagnostic and prognostic value of hypotension in tuberculosis. His experimental work indicated a possible toxic mechanism acting on nearly all the organic systems, particularly the vasomotor regulating centers. Subsequently, no comprehensive study which definitely indicates that the incidence of hypotension is higher in patients with tuberculosis than in the general population was found in the literature of the English-speaking countries. Nearly all discussions of hypotension include tuberculosis as one of the important causes[10,41,44,45,85,99,105], however, and associate it with activity of the disease[142]. Tuberculosis of the adrenal glands is thought by many to be the cause of the hypotension, but the latter is sometimes present even in the absence of the former. Loss of tone, psychic depression, and chloride imbalance undoubtedly play some part. Much emphasis has been placed upon the inter-relation between hypotension and tuberculosis, but this has not been substantiated by facts.

From the list of clinical conditions associated with *postural hypotension*[120], it is obvious that this is not itself a clinical entity but is merely a manifestation of the disturbance in reflex control of the cardiovascular system. Diseases of the nervous system which have been reported to effect this disturbance are: combined sclerosis of pernicious anemia, disseminated sclerosis[80], syringomyelia, arteriosclerotic degeneration disseminated throughout the nervous system[84], multiple encephalomalacias[57], Parkinsonism[92,144], Ménière's syndrome[96], influenzal encephalitis[75], tabes dorsalis[80], dementia paralytica[43], sympathetic ganglionectomy in treatment of hypertension[56,80,106], diabetic neuropathy[107], diabetic neuritis[80] and psychic disturbances. Endocrinopathies which may be associated with this disturbance are thought to produce changes in the cells of the hypothalamus[11], hypoinsulinism, hypopituitarism[80], diabetes insipidus, exophthalmic goiter[80] and Addison's disease[11]. Postural maladaptation is also observed in myasthenia gravis[81], peptic ulcer[109], sprue[80] and in a high percentage of dermatologic patients[133].

Management. Since hypotension is not a disease entity, it should not be managed as such. Essential asymptomatic hypotension discovered on routine examination warrants investigation to determine whether it is a manifestation of some underlying disease, but once this has been excluded, it should be accepted as the ideal blood pressure in a healthy individual. In hypotension accompanied by symptoms, a primary cause should be sought. The psychic make-up of those hypopietic individuals who present symptoms with no demonstrable organic pathologic abnormalities should be carefully studied. Unless the underlying problem is a severe neurosis or psychosis, the patient need not be relegated to the care of the psychiatrist but can be managed by the internist or family physician familiar with the problem involved[10]. The low blood pressure encountered in the asthenic states will probably rise as the patient's general condition improves[59], and usually the less said about the blood pressure the better, as the patient may consider the alleged deviation from normal as a grave indication. It is a mistake for the physician to offer these individuals an excuse for perpetuating their symptoms and accentuating their asthenic state; reassurance and sound psychotherapy are the most rewarding therapeutic procedures for alleviation of symptoms.

Constant supervision with attention to adequate nutrition, especially in those cases associated with anorexia nervosa and other cachetic states[123], exercise and improvement of existing enteroptoses by abdominal binders and other methods[136] are beneficial. Drugs, such as benzedrine, epinephrin, ephedrine, paradrine, pitressin, ergot or other tonic drugs, are usually of little permanent value but occasionally offer temporary symptomatic relief, especially if they restore the subject's energy and confidence. Thyroid and commercial extracts of adrenal glands are probably of no assistance[72].

The hypotension associated with various disease states may be approached by attempts to correct the altered physiologic conditions. In cases of diminished levels of sodium or chloride in the blood, administration of sodium chloride along with desoxycorticosterone may be warranted[52,120,141]. When hypoglycemia is encountered, glucose is indicated[9]. Necessity for treatment of anemic states is obvious, as is that of toxemias of infectious diseases by specific therapy.

Treatment of postural hypotension presents a special problem. MacLean[79] recommends having the patient sleep in a head-up position in an attempt to allow physiologic readaptation to the erect posture. Abdominal binders or leg binders[65], various pressor drugs[16,22,65], avoidance of exercise on warm days, and use of added salt and desoxycorticosterone[52] have all been suggested.

It cannot be overemphasized that management of hypotension should not be directed primarily at the blood pressure but rather at correcting the underlying cause, whether it be organic or functional. Elevation of the blood pressure without psychic stimulation has proved ineffective in the relief of symptoms[39]. Asymptomatic essential hypotension requires no treatment and should be regarded as the ideal pressure.

Summary and Conclusions. The literature concerned with hypotension has been reviewed and some of the important physiologic mechanisms responsible for its presence have been presented. An effort was made to correlate clinical findings with physiologic changes producing the symptoms and signs frequently associated with hypotensive states.

Though the terms "hypotonic" and "asthenic" have been freely used, it should be reiterated that any factor, psychic, physical, chemical, physiologic or pathologic, manifests its effect on the blood pressure only by its alteration of blood volume, peripheral resistance, cardiac output, size of the vascular bed or viscosity of the blood.

The fundamental clinical point to be gained by such a discussion is one which has previously been stressed many times: that hypotension is not a disease but rather is sometimes the manifestation of an altered physiologic state and sometimes the ideal level of blood pressure, suggesting freedom from cardiorenal disease and a promise of increased longevity.

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NEUROLOGY AND PSYCHIATRY

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NARCOLEPSY: BRIEF REVIEW AND REPORT OF CASES

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A conservative estimate[7] is that one-third of all patients who seek medical advice are victims of some disturbance of sleep. Although the majority of these patients suffer from insomnia, a sizable percentage complain of excessive drowsiness or sleepiness. This paper is concerned with a well-defined part of the latter category, narcolepsy, which compensates for its relative infrequency by its habit of invading and pervading most of the medical specialties with its bizarre symptomatology. The term "Narcolepsy" (Gr. narkë, sleep, and lepsis, a seizure)[40] was proposed by Gelineau in 1880 for what he considered "a rare neurosis characterized by an urgent need to sleep, sudden and of short duration, recurring at more or less close intervals"[30]. While thus naming the so-called "neurose rare" descriptively for the irresistible attacks of diurnal sleep, he also included in the clinical syndrome attacks of complete muscular tonelessness, either type of episode occurring spontaneously or precipitated by profound emotion. Emotionally induced loss of muscle tonus was named "cataplexy" (Gr. kata, down, and plessein, to strike)[40] in 1902[58,16]. Since Gelineau's memorable paper "De la Narcolepsie"[30] was published, several hundred cases similar in symptomatology to those which he presented have appeared in the literature. Many excellent general reviews of the subject have been written[43,16,58,9,61,67,18]. Most authorities on the subject now look on narcolepsy as a symptom-complex rather than a distinctive disease entity[34]. Some reserve the diagnosis of narcolepsy for cases showing both the sudden attacks of diurnal sleep and cataplexy. This is the true or classical "Gelineau Syndrome". Others feel that in the present state of our knowledge, lines of differentiation should not be drawn too sharply[16,17]. As a result, cases of narcolepsy reported in the literature may be "with or without cataplexy", depending on the interpretation of the individual writer.

The symptom-complex of narcolepsy may consist of all or only a few of the following symptoms[9,16]: *1.) Attacks of diurnal sleep.* This symptom is the single "sine qua non" for the diagnosis of narcolepsy, and is usually, but not necessarily, the most troublesome manifestation to the patient. Characteristically the attacks of sleep are abrupt in onset but may be preceded by a short period

of drowsiness which barely allows the patient time to retire to a safe or comfortable place for the oncoming attack. Patients so afflicted have fallen asleep while driving an automobile, while walking, talking, sitting at the dinner table, reading and so on. The situation in which the patient falls asleep is often one that is conducive to sleep in the normal individual. The actual sleep is clinically indistinguishable from normal sleep and can be terminated in the same manner with equal ease. A previous good night's rest or prolonged sufficiency of nocturnal sleep has no effect whatsoever on the urgency, frequency or length of subsequent sleep attacks. These episodes may occur from once or twice a week to as many as 200 daily. They last from a minute or two to an hour or so and leave the patient feeling keen and alert on awakening. 2.) *Cataplexy*[29]. Cataplexy usually consits of a sudden complete loss of tone of all the voluntary muscles of the body, beginning with the muscles of mastication. An overwhelming majority of these attacks are precipitated solely by jokes or humorous situations which evoke maximum sudden unexpected laughter in the patient. His jaw drops. His knees can no longer support his body, and, in a few seconds, he is like a mass of jelly lying on the ground, conscious but unable to talk or move. Within a minute or two he regains full use of his muscles and is normal in every respect. Less commonly cataplectic attacks may abruptly follow the emotional stress incidental to anger, fear, excitement, surprise, or weeping, or rarely may occur spontaneously, apparently unassociated with any specific emotion. Cataplexy usually has its onset at the same time as, or a few months later than, the sleep attacks. Cataplexy is very rarely a solitary symptom. 3.) *Sleep paralysis*[11,70]. This symptom consists of a brief period of complete inability to move or talk immediately preceding or following diurnal or nocturnal sleep. Consciousness is usually distressingly clear and the patient suffers acutely from fear of impending death or other disaster. The attack lasts from a minute or two to an hour or so and can usually be terminated at once by the simple touch of another individual. Sleep paralysis is a much less frequent concomitant of the narcoleptic symptom-complex than cataplexy, and occurred in only 8% of one series of 200 cases of narcolepsy[9]. Terrifying dreams often seem to precipitate those attacks of sleep paralysis which begin in the middle of the night or immediately after awakening in the morning. 4.) *Disturbed nocturnal sleep.* The nocturnal sleep of about 80% of narcoleptics is disturbed by insomnia, terrifying dreams, somnambulism, or somniloquism. 5.) *Hypnagogic hallucinations.* These consist of vivid stereotyped frightening dreams which are experienced in the half-awake state. They sometimes occur just prior to or during an attack of sleep paralysis and are rarely an isolated symptom. Hypnagogic hallucinations may persist for a short period into the partially or fully awake state and result in severe anguish and anxiety. 6.) *Paranoid psychotic state*[9,51,61]. Rarely, a chronic hallucinatory paranoid state seems to develop on the basis of the dream experience. 7.) *Gain in weight*[15]. In one large series of cases[16] almost half of the patients gave a history of a disproportionate gain in weight after the onset of narcolepsy. This tendency was more marked among women[37]. 8.) *Transient diplopia or transient ptosis*[81]. Although this symptom is not peculiar to narcoleptic patients it is occasionally seen prior to the sleep attacks or even independently of them. 9.) *Impairment or absence of libido.* This is found in 10 to 15% of the cases. 10.) *Headaches.* When present,headaches tend to appear immediately before attacks of sleep

particularly if the latter are resisted, and are often completely relieved if the patient is allowed to sleep and awaken without interference.

Narcolepsy may be classified etiologically into the following groups: 1, *Idiopathic Narcolepsy.* Over one half of all cases of narcolepsy fall into this category and hence yield no evidence of organic disease. 2, *Symptomatic Narcolepsy.* This type follows tumors, inflammations and degenerative conditions involving the hypothalamus[15,65]. Sleep attacks alone, or in combination with cataplexy, are especially common after encephalitis[58]. Other diseases and conditions which are sometimes associated with the symptom-complex are: central nervous system syphilis[50], head trauma[38,58], cerebral arteriosclerosis, polycythemia vera[61], diabetes, hyperinsulinism, acromegaly and multiple sclerosis. 3, *Cases associated with endocrine dyscrasias.* This is a presumptive explanation used in cases associated with obesity, alterations in metabolism and other symptoms suggestive of endocrine abnormalities. 4, *Cases complicating convulsive (epileptic) attacks.* 5, *Cases apparently of psychogenic origin.* This category includes those associated with hysteria[76], and other neuroses, as well as the major psychoses[18].

There is abundant clinical[4,37,84] as well as experimental evidence[59] that lesions of the hypothalamic nuclei and surrounding regions may cause hypersomnia and, or, narcolepsy[53,73,87,18]. Some authors have even postulated a "sleep" or "waking" center in this area[59]. The fact that man is able to fall asleep in a conscious or unconscious attempt to escape certain emotional difficulties, or to remain awake during emergency situations and periods of emotional stress, suggests that the higher cortical centers also play an important role in the regulation of sleep. The hypothalamus is in intimate connection, by means of its pathways, with the cortex, thalamus, basal ganglia, and brain stem. Disturbances of sleep seem to result when the integration of this complicated mechanism is disrupted by destructive or irritative lesions or by emotional factors[18]. Hence, sleep is a function of the whole person[23,22]. Much scientific research has been done in an effort to determine if definite emotional constellations precipitate or aggravate the neurophysiological disturbances responsible for the manifestations of narcolepsy[13,18,45,54,71]. Every emotional situation is invariably associated with some physiological response such as sweating, palpitation, shortness of breath, pallor, blushing, blood pressure changes, erection of hair, sphincteric disturbances, laughing, weeping, sleeplessness or somnolence. Until recently medicine has paid little attention to the investigation of these processes as they were considered a part of normal life, common to everyone, and hence without ill effect. However, it is common knowledge now that persistent emotional disturbances may result in chronic bodily changes such as hypertension, peptic ulcer, asthma, mucous colitis and so on[52]. These physical responses apparently are mediated and controlled by the hypothalamus (a vegetative center) as well as by the cortex and possibly other subcortical structures[18]. The symptom-complex of narcolepsy has, in various patients, been found to be associated with repressed conflicts involving hostility[27], guilt feelings, dependency needs, or various disturbed relationships between the patient and his environment[13]. The symptoms often appear to be neurotic defenses against anxiety, with symbolic significance[45].

Many conditions must be considered in the differential diagnosis of idiopathic narcolepsy. First and foremost among them is idiopathic epilepsy. Gelineau expressed the opinion that

epilepsy and narcolepsy are unrelated. He said, "Peut-on voir là de l'épilepsie? Je ne le pense pas"[30]. That is still the view of most writers on the subject[82]. However, in most textbooks one finds narcolepsy discussed among the "convulsive disorders", "disorders of sleep", or perhaps even among "the epilepsies", primarily because of the difficulty in classifying this symptom-complex. The following are some of the similarities between narcolepsy and epilepsy: 1.) Psychoanalytic research indicates that in both conditions the symptoms inhibit, deflect, and prevent awareness and action which threatens to disrupt consciously accepted patterns of behavior[13]. This is best exemplified in cataplexy. 2.) A small percentage of patients are both epileptic and narcoleptic[17,46,61]. 3.) An occasional case of narcolepsy has a positive epileptic heredity[61]. 4.) Both are characterized by periodically recurring attacks which begin abruptly and are of "relatively short duration"[16]. The following are the even more striking differences between narcolepsy and epilepsy: 1.) Most of the authoritative evidence indicates that there is nothing in the character of the electrical discharges from the brain of the narcoleptic patient which would link them with the abnormal electrical discharges from the brain of the epileptic patient[12,19,62,33]. Most authorities agree that "the sleep records of narcoleptics are like those of normals except that the decline to a deep level of sleep is more rapid[10,32,58,21]. The electroencephalogram is usually normal in idiopathic narcolepsy during "the awake period"[15]. Symptomatic narcolepsy is much more likely to show other electroencephalographic abnormalities. 2.) Mental deterioration is a frequent sequel to epilepsy characterized by frequent seizures, and the seizures vary markedly in frequency throughout the life of the patient[30,79]. Patients with idiopathic narcolepsy, on the other hand, suffer from no intellectual impairment, regardless of the frequency of their attacks; and, in untreated cases, the number and severity of the attacks are much less subject to amelioration or exacerbation[16]. 3.) Narcoleptic attacks are not accompanied by convulsive movements, biting of the tongue or cheeks, or loss of bladder or bowel control. After a sleep or cataplectic attack the patient is usually alert[30]. In cataplexy there is usually conscious awareness of environmental sounds and events in spite of the relative or absolute muscular immobility and inability to speak. The fact that cataplexy is emotionally precipitated is usually obvious to the most untrained observers and acquaintances of the patient. 4.) The commonly used anticonvulsant drugs[42] are completely ineffective in relieving narcoleptic attacks. 5.) The diurnal sleep attacks of narcolepsy (except for their abrupt onset) are similar in every respect to normal physiological sleep, and can be terminated with equal facility.

The differentiation of idiopathic narcolepsy from narcolepsy secondary to organic disease, endocrine dyscrasias and psychogenic factors will naturally depend on the individual physician's proficiency in the diagnosis of those conditions. Other diseases and conditions which must be differentiated are: coma from any cause, hookworm disease, trypanosomiasis, the drowsiness of fatigue, the lethargy of convalescence from febrile illnesses, the fatigue common to chronic wasting diseases, the somnolence of asphyxia, the drowsiness or somnolence of over-sedation, and acute alcoholism[84]. Probably the most important consideration is for doctors to keep in mind the possibility of narcolepsy in their differential diagnoses. Clinical guesses frequently made on narcoleptics have included over-drinking of milk, neurocirculatory asthenia,

laziness, and disbelief in the patient's statement[35].

There are several interesting military aspects of narcolepsy. As a "disturbance of consciousness", it is a cause for rejection for military service[2]. Since idiopathic narcolepsy occurs several times more often in males than in females, and usually has its onset before the age of 25, it is apparent why many cases of this symptom-complex have appeared among military personnel[26,56]. Soldiers on guard duty who fall asleep while in the performance of this important function are usually subjected to disciplinary action[34,67]. (This has been considered a major military offense by all armies down through the ages.) In some cases, however, a defense on medical grounds is appropriate and just. During World War II, one psychiatrist[49] reported that "Of 25 soldiers discovered asleep on post as sentinels, they were divided into the following 3 groups: *a*, Four men were rebellious psychopaths who fell asleep intentionally. *b*, Nineteen men were, in the main, good soldiers, who fell asleep because they more or less carelessly had failed to get enough sleep before going on post. *c*, Two men had narcolepsy." A War Department publication on the subject of military training[83] advises that "morning hours should be used for training requiring the greatest mental concentration. Afternoons are suited to subjects requiring action and movement". Interestingly enough, narcoleptics have a tendency to develop sleep attacks during the same monotonous or post-prandial periods which ordinarily cause drowsiness in the normal individual. Then, too, the narcoleptic can often dispel drowsiness, at least temporarily, by physical exertion. Since narcoleptic symptoms are bizarre, the victim of such a condition in the military service is often at first called "lazy" or "Rip Van Winkle", reduced to the grade of private for falling asleep during lectures and demonstrations, and given more and more menial assignments. However, since even top-sergeants have a limit to their endurance, the narcoleptic eventually is sent to the hospital. There is certainly some similarity between cataplexy and the condition of some combat soldiers who become "paralyzed" by fear. "This fear paralysis is also seen in animals, as when a small animal is unable to escape from an approaching snake"[77]. Another writer[86] stated that "It must have meant safety to the animal to lie motionless as though dead. From this aspect at least, the phenomena of the affective cataplectic fit fall into line with reactions phylogenetically ancient, and are capable of psychological and teleological explanation. It would appear that the mechanism once utilized by fear to produce motionlessness can also be activated by an emotion of opposite quality." The most decorated American soldier of World War II, in his realistic book, "To Hell and Back"[57], tells of the unexpected appearance of two German soldiers at the front during the Italian campaign. Of the incident he said, "As we prepare to leave, two straw-laden figures round the stack. For an instant, the four of us stand stupidly sharing a mutual paralysis of surprise. Then, still clutching our straw, we take off." Another author[49] stated that "Soldiers brought up to the front line have fallen asleep under their first bombardment. The experiments of nature duplicate Pavlov's on conditioned inhibition. When a man perceives a peril from which he wants to escape, but is deterred by some other circumstance such as the wish to appear brave, he is being acted on by an 'inhibitory combination' of stimuli: excitations which under simpler conditions would be given free rein are now checked by an inhibitory process. Narcoleptics betray an undue susceptibility to inhibition." Several cases of sleep paralysis are

reported to have occurred in "returned Air Force personnel suffering from combat fatigue. The condition occurred singly, not in association with cataplexy, narcolepsy, or somnambulism. Superficial analysis led to the impression that sleep paralysis is, in all probability, related to a state of confusion as to emotion and intention, with resulting indecisiveness"[80]. Another writer stated that "In sleep paralysis sleep does not normally spread rapidly and diffusely through the nervous system, but the motor and postural centers fall asleep before the mind, or in awakening the mind awakens before the body; in somnambulism the reverse occurs—the motor and postural centers are active while the mind is asleep"[8]. It has also been reported[47] that hypnagogic hallucinations are at times found in the early stages of war neuroses.

Amphetamine (benzedrine) sulfate and ephedrine sulfate are the drugs of choice for the treatment of narcolepsy. A tremendously large literature has accumulated on the effectiveness and action of each. Most authorities feel that benzedrine is the more effective drug[1,7,17,22,58,62,67,75]. Several writers have agreed that ephedrine is often more effective in controlling the attacks of cataplexy than the attacks of sleep[7,58]. One report[20] stated that 6 patients obtained symptomatic relief from the sleep attacks as well as the cataplectic attacks by the combined oral administration of potassium chloride (10 grains after each meal) and benzedrine sulfate (10 grains, 2 or 3 times daily). Apparently, potassium chloride was considered effective against the cataplectic component (and in one case also against the sleep paralysis), and benzedrine against the sleep component. One writer states that "Alternate doses of amphetamine and ephedrine may be efficacious in some cases"[1]. Benzedrine has been advocated as an addition to the usual anticonvulsants in cases of epilepsy complicated by narcolepsy[46]. Dexedrine sulfate, the dextrorotatory isomer of benzedrine sulfate, is also reported to be effective in narcolepsy but the reports are few in number[18,41]. A few but unimpressive number of cases of narcolepsy have been benefited by oral thyroid extract[16]. Other drugs which have been tried, largely with little or no benefit, are caffeine, strychnine, irradiated ergosterol, theelin, and pituitary extracts[20]. Benzedrine sulfate was first introduced in America for the treatment of narcolepsy in 1935[64,74]. As the result of a great deal of research[28,39,44,58,14] we know that the main contraindications to benzedrine are hypertension, coronary disease, manic excitement, and severe exhaustion[75]. There is also good evidence that serious addiction or habit formation do not occur with benzedrine, even after its daily ingestion for many months to several years[5,74]. Symptoms of overdosage of or individual intolerance to benzedrine include hyperexcitability, restlessness, dilated pupils, inability to relax, dizziness, nausea, vomiting, and insomnia[41,64,75,82]. The (unlikely) possibility of benzedrine precipitating a psychosis is raised by one author[88]. A suicide[31] and an accidental fatal poisoning with benzedrine have also been reported. The average oral dosage of benzedrine for the treatment of narcolepsy in adults is 10 mg. 3 times daily, the first 2 doses before breakfast and lunch, and the last dose not later than 3:30 P.M. in order not to interfere with natural nocturnal sleep[64,67,69,82]. The exact dosage will depend on the age of the patient and the severity of the disease. As there is individual variation in response to benzedrine, it is best to start with a total daily dose of 10 mg. and gradually increase it until the optimal effect is obtained. When using ephedrine sulfate, the plan of treatment is to prescribe the oral administration

"of a capsule containing 25 mg. of ephedrine sulfate before breakfast, before lunch and at 4:30 P. M. If the patient is not entirely relieved, the morning and noon doses are increased to 50 mg., but the late afternoon dose is kept as low as possible, and in some instances is omitted, in order to avoid disturbing nocturnal sleep. A few patients have taken as much as 75 mg., while others have obtained relief from 16 mg."[16]. L. E. Daniels (at present Professor of Neurology at Colorado University School of Medicine) and an associate were the co-discoverers of the use of ephedrine in narcolepsy[16]. The symptoms of overdosage of ephedrine are tachycardia, tremulousness, hyperexcitability, and insomnia[75]. However, severe reactions to ephedrine are uncommon[72]. As there is increasing evidence that the psychogenic element is large in some cases of narcolepsy, many cases of the treatment of this condition by psychotherapy have been reported[15,34,55,80], often with marked amelioration of the patient's symptoms or an actual cure[48,61,76,78,18]. F. G. Ebaugh[22], in his training of students and psychiatric resident physicians, has always emphasized the importance of treating the patient as a whole rather than as a system of isolated organs or emotions. The handling of cases of narcolepsy exemplifies the necessity of such a plural approach. The following cases of narcolepsy were diagnosed and treated in one of the hospitals or clinics of Colorado Medical Center:

Case 1. A. L. M., a 13-year-old white boy, was first seen in the Pediatric Neurology Clinic of Colorado General Hospital in July, 1946, complaining of frequent irresistible attacks of diurnal sleep and "falling down spells" of 2 months duration. The "falling down spells" were always preceded by laughter at some humorous situation and caused the patient to fall to the ground and remain there for a minute or two. He was always conscious while on the ground but could neither talk nor move. For several weeks after the onset of his illness he suffered from "dreams of terrible things in which humans took part. He was restless at night and tore up his bed and bed clothes and talked in his sleep for a while." The following examinations and tests were negative: General physical and neurological examination, electroencephalogram (patient awake), spinal fluid, Roentgen-ray examinations of the chest and skull, basal metabolism (-9), blood counts and hemoglobin, blood sugar and nonprotein nitrogen, blood Wassermann and Eagle Flocculation Test. There was no history of head trauma or disease suggestive of encephalitis. Benzedrine sulfate (beginning with 2.5 mg. B. I. D. and gradually increased to 15 mg. B. I. D.) was not very effective in reducing the sleep or cataplectic attacks. Oral ephedrine sulfate (¾ gr. T. I. D.) was more effective but not entirely satisfactory. Inquiry into the home situation revealed that the patient's symptoms began one week following the remarriage of his father. The boy openly resented this newcomer to his father's household. The stepmother considered the boy "stubborn and undisciplined" and felt it her duty to "train him right." The neurologist, the pediatrician and the psychiatrist were equally convinced that the constant "tug of war" between the boy and his stepmother would have to be resolved before treatment with any medicine could be effective. Psychotherapy was advised but the stepmother was extremely defensive, on the grounds that "What he needs is to get away from the hospital atmosphere. I'll handle this situation."

This is a typical case of idiopathic narcolepsy with a probable emotional component as the precipitating or aggravating factor. We know that the emotions affect the symptomatology of organic as well as of functional diseases. For example, the tremors of Parkinson's Disease are markedly increased by anxiety.

Case 2. J. W. S., a 12-year-old white boy, was first seen in the Pediatric Neurology Clinic of Colorado General Hospital in July, 1946, with the following complaints: "I have had sleeping spells for a year now, 3 or 4 times a day. They come on usually when I ain't got nothing to do. The other kids think it is funny when I fall asleep in school, but I don't think it is funny. My teacher makes me stand up to keep me awake. Walking will keep me awake. I sleep for a minute or two up to an hour or so. I don't sleep well at night since these sleeping spells

began but never dream. About two weeks after the sleeping spells began I was running home after a drum lesson. It was raining and I wanted to get home before I got too wet. I slowed down in the middle of a street and then just collapsed. I didn't know what had happened but got up right away. I hadn't been laughing or anything. The next day at the dinner table Dad told an awful funny joke. My whole head collapsed on my chest and my jaw opened. I couldn't talk a bit. My eyes were open and I could see and hear everything. It lasted half a minute and scared my folks. I have never fallen out of a chair in those spells. I have only skinned my knees a couple of times from falling down. I fall down any time of the day when I laugh hard at something funny. First my jaw opens wide and then my legs get weak and then, bam, I drop to the ground in a heap. It all takes only a few seconds. My eyes are shut while I'm falling but as soon as I hit the ground I can open them. I can see and hear everything that is going on during a spell. In school I put my handkerchief in my mouth to keep from laughing or put my hands over my ears to keep from hearing the jokes. It usually works. When I'm swimming and get to laughing my jaw drops down and I swallow a lot of water. So I turn over on my back and float until my jaw gets strong again. The other night I was just talking to some guys and I wasn't laughing or thinking of anything funny, just talking natural. All of a sudden my knees and jaw got weak. I asked the fellows real fast to hold me up, but they thought I had a disease that was catching and took off and never came back. It was at night and I hit the ground. I knew what was going on and could even move my arms and legs a little but not enough to get up. After a minute I could sit up. In another half minute I was as strong as ever." He denied attacks of sleep paralysis, somnambulism and somniloquism. There was no history of head trauma or encephalitis. The only childhood diseases which he had had were chickenpox at 6 years and measles at 7 years, both mild and uncomplicated. Physical and neurological examinations were and still are negative except for eczema of the face. At present, he is 65 inches tall and weighs 130 pounds. He is well proportioned and his body configuration shows no evidence of endocrine disorder. The following examinations were negative: Repeated urinalyses, blood counts and hemoglobin, blood sugar and nonprotein nitrogen, blood Wassermann, spinal fluid, Roentgen-ray examinations of the chest and skull. The electroencephalographic report of December, 1946, stated that "The sudden appearance of short bursts of sleep waves is like that frequently seen in narcolepsy." He was started on amphetamine (benzedrine) sulfate, 2.5 mg. T. I. D. (after breakfast, lunch, and at 3:00 P. M.). This dosage was gradually increased to 15 mg. T. I. D. and was sufficient to prevent 90% of both the sleep and cataplectic attacks.

His past history revealed that he has suffered from severe eczema since the age of 3 months and that he has been treated for this condition almost continuously since then. Other children were afraid of "picking up his skin disease," but in general accepted him until he developed narcolepsy. Within a year after the sleep attacks appeared, the patient resigned from the Boy Scouts, the Y. M. C. A., and the school band as he felt that all of his friends had deserted him. He has no affection for his father, who divorced his mother in 1939, and in fact is very hostile toward him "for the bad beatings he used to give me over nothing." His mother has had to work outside the home since 1941 in order to support her four children. "The children have had to raise themselves since then." Within a few months after the onset of narcolepsy the patient developed a marked change in personality. He was placed on probation by the Juvenile Court for stealing money from his father and for collecting money from other boys' paper routes. He became increasingly irritable and threw knives and ice picks at his older brother. He played truant from school at frequent intervals and ran away from home several times. Because of these difficulties both the patient and his mother were treated at the Mental Hygiene Outpatient Clinic of Colorado Psychopathic Hospital at regular weekly periods, beginning in February, 1947. The patient was treated for 5 months, with moderate improvement in his behavior difficulties. However, the mother stopped her own treatment after a few interviews "because this is my son's problem, not mine, and besides I have to work every day". Brief psychological testing more than 2 years ago revealed "A full I. Q. of 74 (classification, borderline defective). The Brown Personality Inventory for Children shows a poor home adjustment, insecurity, irritability and undue concern over his physical well-being."

One year ago, the patient quit school because of poor grades. Since then he has worked at various odd jobs for a few weeks at a time. He talks from the corner of his mouth with the appearance and accent of a "Dead End Kid." Psychological tests[6,66] (The Rorschach and Thematic Apperception Tests), interpreted by a clinical psychologist[63] of

Colorado Psychopathic Hospital's Department of Psychology, revealed the following: "The diagnostic impression is a neurotic depression. In his stories the mother is a hostile rejecting figure. He tends to solve problems by evading them. He is resigned to his father's hostility and reacts to its passively. He is afraid to strike back. It is interesting that in some of his stories he evades striking back at men by going to sleep."

This also is a typical case of idiopathic narcolepsy. Unfortunately it was engrafted on a personality already crippled by the frustrations of a lifelong disfiguring eczema and borderline mental deficiency. In spite of it, however, this patient can probably be kept from being a menace to society, by medical and psychotherapeutic measures available to the general practioner[25].

Case 3. J. D. E., a 14-year-old white boy, was first seen in the Pediatric Neurology Clinic of Colorado General Hospital in February, 1949, complaining of "headaches, sleeping and falling spells". His mother said: "Since June, 1948, he has fallen asleep about 6 times every day, usually when he sits down and has nothing much to do. He closes his eyes and is asleep just like that (snapping her fingers). He never falls asleep outside when he is doing the chores, only when he comes inside. He has complained of rather sharp headaches also since June, 1948, and nothing but sleep will stop them, not even aspirin. He never has headaches at night. I usually have to shake him a little and call him to wake up. He wakes up in about a minute, and is usually cranky if I wake him up before he has slept about 20 minutes. He often falls asleep while he is reading. It looks like ordinary sleep to me. He has even gone to sleep while he is sitting at the supper table, but never during an interesting discussion. He goes to sleep instantly. Five months after his sleeping attacks began, his falling attacks started. Whenever he hears a funny joke and laughs out real hard his arms and legs just kinda dangle and he falls to the ground. His knees just give away and it is a minute or two before he can get up. While he is there on the ground, his eyes are open and his jaw is dropped. He would make kind of a funny noise with his throat like he was still trying to laugh but couldn't get it all out. He never gets unconscious or soils his clothes. He never twitches or jerks during these spells and always hears the end of the joke that he was listening to. He never goes to sleep after the spells." The patient said, "The headaches are sharp and just on one side, from the right side of my nose to the right middle part of my head, not often on the left side. I have the headache every day, sometimes in the morning and sometimes in the afternoon. It is not usually severe. It stays 10 or 15 minutes and sleeping stops it mostly. Even with aspirin I have to sleep to stop it. I feel sleepy for a while before I fall asleep. Getting up and running is the only way I know to stop the sleep, or if somebody teases me real strong. If I stay out of breath I won't sleep but fall asleep when I stop breathing hard. If I just trot I'm still sleepy but if I run with all my might I'm not sleepy. I stay asleep 1 to 1½ hours and feel fine when I wake up. I never sleep after laughing real hard. I never go to sleep while I'm walking. I usually fall asleep when I ain't got nothing to do or when I'm not interested. At school it is usually in the afternoon when I fall asleep as I don't like the teacher. I get mad when anybody wakes me up. Last summer for a while I used to wake up at night scared and in a cold sweat as I would dream of monsters or snake pits. But now when I dream it is about going to school or something like that, not scary. I never walk or talk in my sleep. I sleep 8 to 10 hours every night, but sleeping more does not keep me from getting sleepy in the day. The falling down spells are much more trouble to me than the sleeping. I start to laugh, get out a few laughs and then lose control of my muscles all over and I just fall down. I stay down for a minute or so and know everything that is going on around me. I can hear them talk and can see them walking around. Once in a while, though, while I'm down my mind isn't real clear and I get clouds over my eyes and I can't see real well. When I get control of my muscles the cloud goes away from my eyes and I'm all right. Shaking me or talking to me brings me out of it. Mom always says, 'Stop that'. I fall whenever I hear a real funny joke and sometimes I feel weak after it and have to sit down for a while, but not most of the time. Laughing is the only thing that makes me fall but when I cry real hard when I'm mad, my knees get weak for a few minutes. I also get weak knees when I get mad at our calf for running away from me, but I don't fall. That calf sure makes me mad when he runs off. When I laugh hard at school, when I'm sitting down, my arms drop to my sides and my head hits the desk with a bang and that snaps me out of it and I'm all right. The same thing happens if I fall asleep in

my seat. I fall down from laughing any number of times a day, depending on how many times I laugh. At school, the kids sometimes try to make me laugh to see me fall. They think it is funny. To keep from falling down I try not to laugh and put my chin down on my chest. If I push my chin down on my chest and shake my head I just fall down to my knees and then get right back up. I have never hurt myself falling down. Sometimes I can't concentrate lately, for example when a kid makes a noise. My memory might be a little poor as I forget things easily that I have done, especially in History or in English. I have to get up every night to urinate since the sleepiness began." He denied symptoms of sleep paralysis.

Physical examination was essentially negative. He is 65 inches tall and weighs 143 pounds. He has gained 15 or 20 pounds of weight during the past year. He has adult type genitalia and a moderate amount of public and axillary hair. He is heavily muscled and well proportioned. He appears at least 2 years older than his stated age. He is left handed. Mental status examination revealed a sober-faced boy of 14 years who neither smiled nor laughed. He seemed to be of about average intelligence and carried on a normal conversation. His words and accents smacked of a farming community. There was no evidence of psychosis. Psychological tests[63] revealed "a Full Scale I. Q. of 92, a Verbal Scale I. Q. of 96, and a Performance Scale I. Q. of 91. The classification is average. The subtest scatter and variability of performance of the Wechsler-Bellevue suggest a neurotic impairment of functioning rather than organicity. The Rorschach suggests an obsessive-compulsive neurosis. His stories, in the Thematic Apperception Test, describe an overprotective mother on whom the son is extremely dependent. He feels insecure and fears rejection by the mother. He is very hostile to his father, but is afraid to express it for fear of retaliation. If he expressed hostility toward his mother it would threaten his dependency gratifications. The many death stories suggest that he tends to introject his hostility. The stories dealing with sleep, or rest, or unconsciousness, suggest that his narcolepsy may be a useful mechanism for avoiding expression of hostility." The following examinations were negative: Urinalyses, blood counts and hemoglobin, blood Wassermann, blood sugar and nonprotein nitrogen, spinal fluid, Roentgen-ray examinations of the chest and skull, and basal metabolism (−7). The report on the electro-encephalogram was as follows[10]: "Most of the record is a sleep record. This examination presents evidence of a severe diffuse paroxysmal cortical disturbance with the principle disorder in the anterior portion of the cortex."

Birth and developmental history were normal. He had chickenpox at 1 year, mumps and measles at 4, and whooping cough at 6, all mild and without complications. There was no history of high fever, coma or somnolence prior to the present illness. However, according to his mother, when he was 2½ years old he fell backward off a bed and hit his head on the floor. He was not rendered unconscious but "complained of headache across his forehead after that until he was 6 or 7 years old". There were no neuropathic traits. Psychosexual development was normal. He has one brother, 20 years of age, and 2 sisters, one of whom is 16 and the other 10 years of age. His father and mother were divorced 3 years ago. Since then the mother and children have been supported by the County Welfare.

Treatment consisted initially of oral ephedrine sulfate (gr. ⅜ before breakfast and lunch). Two weeks later another gr. ⅜ capsule was added to the daily dosage, at 4:30 P. M. The cataplectic attacks were almost completely abolished, and the sleep attacks were reduced to about one daily, always after the evening meal. Perhaps at a later date he will be tried on benzedrine sulfate. However, ephedrine sulfate has almost abolished his chief complaint, the cataplectic component.

This case also presents the classical symptoms of idiopathic narcolepsy, but the history of head trauma[34] and the abnormal electroencephalogram findings cast some doubt on the "idiopathic" etiology. However, the question is of purely academic interest as the treatment is the same in either case[17].

Case 4. L. R. K., a 16-year-old white boy, was admitted to Colorado General Hospital in June, 1947, because of sleep attacks and "falling spells" of one year's duration. Both types of attacks started about one month following the onset of an exceptionally severe case of acute infectious hepatitis. His sleep attacks occurred 5 to 6 times daily and were typical in every way. The cataplectic attacks also were typical and followed immediately "whenever he got excited or laughed real hard about something". General physical and neurological examinations, as well as the following, were entirely negative: Urinalyses, blood counts and hemoglobin, blood sugar and nonprotein nitrogen, blood Wassermann,

spinal fluid, and Roentgen-ray examinations of the chest and skull. The initial dosage of amphetamine (benzedrine) sulfate of 5 mg. after breakfast and after lunch was increased to 10 mg. twice daily. This latter dosage abolished the attacks of tonelessness following laughter and diminished the sleep attacks to about one daily. A recent follow-up report shows that the patient is doing very well in high school and will graduate this year. He is a star member of his school football team.

This is apparently a case of symptomatic narcolepsy, the result of an encephalitis (or localized degenerative process in the hypothalamus[60]) complicating acute infectious hepatitis[68]. This type of narcolepsy has been reported previously[16]. Involvement of both liver and brain, in acute and chronic hepatic disease, is of common occurrence. Such diseases as Wilson's Disease (hepatolenticular degeneration) and kernicterus are well known examples[3].

Case 5. R. G., a 26-year-old single white male, was admitted to Colorado Psychopathic Hospital in July, 1942. The patient, the son of Mexican parents, gave the following account: "In 1941 I had a quarrel with my girl and her aunt, and her aunt didn't approve of me. I was disgusted and joined the army. About that same time I started getting sleeping and drop spells. When I'd go on marches with my unit I would fall asleep during the short rest periods—also during class periods. I told an officer that I could carry on normally the rest of the day if I could only take a few naps. He got mad and had another soldier slap me whenever I got sleepy. That made me awful mad. They finally sent me to the hospital and I was discharged as having narcolepsy, after being in the army for only 3 months." His parents said, "These sleeping spells last 15 to 60 minutes and occur several times a day, mainly when he is doing nothing in particular but sometimes when he is at the dinner table or while he is talking to someone. The drop spells usually follow temper tantrums when he is mad about something. He just falls down and can't move or talk for a minute or two. He loses control of his jaw and tongue. For years he has been hard to get along with, and argues, and always thinks that he knows everything. For the past year he talks in his sleep at night and has wild imaginations. For years he had the idea that his family doesn't like him."

His past history revealed that the only childhood disease he had had was a mild case of measles at 13 years of age. There was nothing to suggest encephalitis. He gave no history of head trauma. He completed almost 2 years of college, majoring in education. He quit college at the age of 20 because of the development of multiple somatic complaints. No organic disease was ever discovered to account for the complaints. From then until joining the army he was an ineffective helper on his father's farm. After discharge from the army he continued working on his father's farm, and was a constant source of annoyance because of his belligerent and superior attitude. The father is described as a domineering patriarchal type of man who insisted on governing his family with iron discipline.

Mental status examination revealed a seclusive individual with many somatic complaints. He had several sleep attacks daily while in the hospital but no cataplectic attacks. He was irritable and demanding, and believed that everybody was against him and talked about him. He admitted terrifying auditory and visual "hallucinations" at night which took the form of snakes and dragons. His I. Q. was 102. Physical examination was entirely negative. The following examinations were also negative: Urinalysis, blood counts and hemoglobin, spinal fluid, blood sugar and nonprotein nitrogen, blood Wassermann, blood bromide, Roentgen-ray examinations of the skull and gastrointestinal tract, electrocardiogram, basal metabolic rate (−13). On the morning of his 9th hospital day he was started on 5 mg. of benzedrine sulfate orally and was to have received the same dose in the afternoon. However, that afternoon the patient's father signed him out against medical advice before the effectiveness or optimum dosage of the benzedrine sulfate could be determined. The final diagnosis was "Paranoid Schizophrenia with Narcolepsy". Follow-up study revealed that the patient's narcolepsy is well under control with small doses of benzedrine sulfate. However, he is still an ambulatory paranoid schizophrenic who is making a borderline adjustment to society.

The relationship of some cases of narcolepsy and paranoid psychoses has been discussed in the literature[9,16,51,61]. However, the exact relationship is still obscure[17].

Case 6. W. C., a 19-year-old single white male, was admitted to Colorado Psychopathic Hospital in June, 1928, with the primary complaint of frequent diurnal attacks of irresistible

sleep. The sleep attacks had been present since he recovered from a severe case of "influenza" in September, 1925. Cataplectic attacks (which were precipitated by sudden laughter), insomnia, nocturnal restlessness and terrifying nightmares had developed a few months after the onset of the "sleeping spells" and had persisted to the time of his admission to the hospital. Mental status examination was negative except for the patient's "marked tendency to fall asleep during the day". Physical examination was negative except for a central type of facial weakness on the left side. The following examinations were also negative: Urinalysis, blood counts and hemoglobin, blood Wassermann, spinal fluid, Roentgen-ray examinations of the skull, and basal metabolism (+1). The diagnosis was "Chronic Encephalitis with Narcolepsy". At that time, 1928, there there was no known effective treatment for this type of narcolepsy. However, in 1930, immediately after ephedrine was proven to be of benefit, Dr. F. G. Ebaugh administered ephedrine sulfate to the patient in oral dosages of gr. ¾ three times a day. Marked symptomatic improvement resulted. One year later he was attending college and was on the school football team. An attempt was made to contact this patient for a follow-up study, but he had moved out of the state and could not be located.

This case is representative of that type of symptomatic narcolepsy which is secondary to chronic encephalitis[15]. Many such cases have been reported in the literature[61,77]. In general the prognosis in this type of narcolepsy is considered better than in any other type[16]. The behavior disorders[36,54] as well as the narcoleptic attacks[29,58,33] which may appear as postencephalitic residuals often respond favorably to psychotherapy[18,54].

Summary. 1. A review of the subject of narcolepsy is presented. This included its historical background, symptomatology, etiology, pathology, psychopathology, differential diagnosis, electroencephalographic characteristics, military aspects, and treatment.

2. Six cases of narcolepsy are presented. The first two cases are definitely of the idiopathic type. The third case is either idiopathic or secondary to head trauma. The fourth case was apparently secondary to a severe case of acute infectious hepatitis. The fifth case was associated with a schizophrenic psychosis. The sixth case was encephalitic in origin.

3. The second and third cases give the patients' own descriptions of their narcoleptic attacks. In addition, the third case gives a mother's impression of her son's illness. These were included in order to acquaint the reader with the detailed clinical picture of typical cases of narcolepsy.

4. The second and third cases, in addition, were given psychological tests in order to contribute to the present knowledge of the emotional conflicts and personality patterns of narcoleptic patients. There is a definite suggestion in both cases that the narcoleptic attacks were utilized to evade unpleasant emotional conflicts.

5. Psychotherapy at the specialty level was offered to the first two patients, with acceptance and satisfactory results in the second case.

6. It should be emphasized that psychotherapy in many cases of narcolepsy is not beyond the scope of the general practitioner, internist or pediatrician handling the patient[85]. The methods and concepts are clear[24,25], and the amount of human suffering that can be reduced by their proper utilization is great.

7. Although amphetamine (benzedrine) sulfate is usually the more effective drug in the treatment of narcolepsy, its older sister, ephedrine sulfate, is at times more effective, and should not be forgotten in the mad rush for something "new and different."

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PROCEEDINGS OF

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SESSION OF MAY 17, 1949

Production of Convulsions in Rats by Exposure to Ultra High Frequency Electrical Currents (Radar). G. M. Austin, M.D., and S. Horvath, Ph.D. (Depts. of Neurosurgery and Physical Med., and Grad. Sch. Med., Univ. of Penna.). Previous experimental work on the effects of radar pulsations on man and animals, indicated that no harmful effects resulted. This paper deals with the effects of continuous radar pulsations at short distances on a group of 47 rats. The dorsal surface of the head was exposed to a wave length of 12.2 cm. for varying periods of time. Sixteen rats were exposed to a 60 watt energy output at 2.5 cm. distance, and 25 rats exposed to a 90 watt output at zero distance from the skull. In 6 rats the director was focused over the spinal cord. Those rats exposed to a 60 watt output showed clonic type convulsions in a mean time of 2.8 minutes. These rats had an average increase in rectal temperature of 4.2° F. Those exposed to 90 watt output convulsed in a mean time of 1.2 minutes. There was no generalized hyperthermia in these rats. Brain temperature measured in 8 rats showed an average temperature of 110.4° F. immediately after onset of convulsions, although in those exposed to 90 watts there was no associated increase in rectal or thigh muscle temperature.

No pathological changes were found in any of the brains of sacrificed rats severe enough to explain the convulsions. Mild pyknosis, in the Purkinje cells of the cerebellum, in the Pyramidal layer of Ammon's Horn, and in the third layer of the cerebral cortex were the only findings outside of moderate congestion. In those animals with the director placed over the spinal cord, no convulsions were noted, although rectal temperatures occasionally rose as high as 112° F.

It is concluded that a specific rise in the temperature of the brain itself is the most important factor in these convulsions, and a generalized hyperthermia has no bearing on the onset of convulsive activity.

Respiratory and Circulatory Reflexes From the Heart and Lungs Initiated by the Veratrum Alkaloids. Domingo M. Aviado, Jr., M.D., and Robert G. Pontius, M.D. (Lab. of Pharmacol., Univ. of Penna.). Preparatory to the study of respiratory and circulatory reflexes arising from the heart and lungs, the site of action of one of the veratrum alkaloids was investigated. Intravenous injection of the alkaloid has been repeatedly shown to cause reflex apnea, bradycardia and hypotension by acting on receptors in the chest. Almost all previous attempts at localization of the receptors were on open-chest preparations and the observations were on the circulatory reflexes. Catheterization of the different parts of the cardio-pulmonary circulation of anesthetized dogs (morphine and chlorolose) has enabled the localization of the receptors responsible for the reflex apnea.

Injection of veratridine in dose of 1μgm. per kg. into the left or right pulmonary artery or into the artery far

out in the substance of the lung was followed by an immediate apnea and hypotension and bradycardia about 5 seconds later. The apnea is due to the drug action on pulmonary receptors because cold block of the ipsilateral cervical vago-sympathetic trunk eliminated the reflex apnea without noticeably changing the circulatory response. Subsequent warming was followed by the return of the apneic response to the drug. The specific nature of the respiratory effect from pulmonary receptors is noticeable by inhalation into the lower respiratory tract of concentrated veratridine solution in mist form. The cardiac receptors were stimulated as long as a sufficient concentration of the drug could reach the coronary artery. Although their response was predominantly circulatory, they slightly inhibit respiration.

There are receptors in the carotid region exclusive of the carotid sinus pressoreceptors, that respond to veratridine with hyperpnea, bradycardia and hypotension. The chemoreceptors in the carotid body sensitive to cyanide can explain the hyperpnea but not the circulatory effects. The hypotension which is common to the carotid and cardiac receptors was shown by femoral blood flow measurements to be accompanied by vasodilatation.

The reflexes initiated from the heart and lungs by veratrum are different from the previously reported cardiac and pulmonary reflexes. They await further investigation for their physiological significance.

Isotopic Studies of the Biosynthesis of Nucleic Acid Components. II. Allantoin. JEROME D. VALENTINE, M.D., D. WRIGHT WILSON, Ph.D., and SAMUEL GURIN, Ph.D. (Dept. of Physiological Chemistry, Sch. Med., Univ. of Penna.).

It has been demonstrated by Buchanan, Sonne and Delluva (J. Biol. Chem., **173**, 81, 1948.) that glycine, acetic acid, carbon dioxide and formic acid are precursors of the carbons of uric acid in the pigeon. The purpose of this investigation was to determine whether these same precursors contribute carbon similarly to purines in the mammal. Advantage was taken of the fact that allantoin is excreted in the urine of the rat as the end product of purine metabolism and is readily isolated by means of a modification of the usual procedure. After administering to rats compounds labeled with radioactive carbon, allantoin was isolated from the urine, purified and degraded to determine the position of the isotope.

In the first experiment a rat was injected intraperitoneally with isotopic sodium bicarbonate hourly for 7 hours. The allantoin isolated from the urine collected during this period was found to be free from radioactivity. This was to be expected in view of the fact that while bicarbonate has been shown to be incorporated in position 6 in uric acid of pigeons, this carbon is absent in allantoin. Enough radioactive bicarbonate had been administered to cause incorporation in the purines of the body tissues.

In a second experiment, glycine, labeled in the carboxyl position with C^{14}, was mixed with the stock diet and fed to nine rats for a period of 10 days. Allantoin isolated daily from the pooled urines showed increasing concentrations of the isotope. After degradation of the allantoin the isotope was found to be incorporated in position 4. It is apparent, therefore, that glycine is utilized by the rat for purine synthesis in agreement with the earlier results obtained in the pigeon.

The Effects of Intravenously Administered Aminophylline on Cerebral Blood Flow in Man. RICHARD L. WECHSLER, B.S., M.D., LEE M. KLEISS, M.A., and SEYMOUR S. KETY, M.D.

(Dept. of Physiol. and Pharmacol., Grad. Sch. Med., Univ. of Penna.). It is a well known clinical fact that 0.5 gm. of aminophylline administered intravenously will stimulate the brain. It is known to make drowsy patients more alert and to make Cheyne-Stokes respirations more regular. It seemed of interest to study the effect of aminophylline on cerebral blood flow in order to help clarify its mechanism of action.

Ten patients, without any obvious cerebral depression, were chosen at random. A cerebral blood flow was performed according to the nitrous oxide method. Following this, 0.5 gm. of aminophylline in 250 cc. of physiological saline solution was administered intravenously over a period of 20 minutes. While the last 50 cc. ran in, a second cerebral blood flow was performed. Pulse, mean arterial blood pressure and respiratory rates were recorded before and during each flow.

These aminophylline studies gave the following results. There was no change in arterial O_2 content. There was an expected increase in respiration reflected in a decrease in arterial pCO_2 and an increase in arterial pH. There was no significant change in overall cerebral oxygen utilization. There was a striking and highly significant increase in cerebrovascular resistance which resulted in a decrease in cerebral blood flow from a mean of 59.4 to 44.4 cc. per 100 gm. per minute ($P<.01$). With the decrease in cerebral blood flow and the constant cerebral oxygen utilization, the cerebral venous O_2 content decreased from 8.2 to 6.2 vols.% ($P<.01$). Since the cerebral venous O_2 content reflects the O_2 tension of the brain, aminophylline causes an anoxia of cerebral tissue.

The mechanism for these changes is obscure. As expected, hyperventilation occurred, reflected by a significant lowering of arterial pCO_2 and a small rise in arterial pH. A drop in arterial pCO_2 is known to cause a decrease in cerebral blood flow. The maintenance of a constant cerebral venous and therefore brain pCO_2 found in this series may be the mechanism controlling the changes in cerebral circulation.

It was noted that 4 of the patients reacted to the drug with extreme anxiety and other symptoms. Each of these 4 cases had an increase in cerebral oxygen consumption, the mean being a statistically significant rise from 3.7 to 4.6 cc. per 100 gm. per min. The other 6 patients had a statistically significant decrease in cerebral O_2 consumption from 3.9 to 3.3 cc. per 100 gm. per min.

These findings indicate that aminophylline, as used clinically by intravenous administration in doses of 0.5 gm., far from acting as a cerebral vasodilator, produces a marked constriction of cerebral vessels and a real anoxia of cerebral tissue as reflected in the constant and striking decrease in cerebral venous O_2 content.

Serum Esterase Levels in Alcoholic Patients. T. C. BARNES, M.D., K. R. BEUTNER, M.D., and R. BEUTNER, M.D. (Hahnemann Med. Coll. and Hosp. of Phila., and the Keeley Institute, Dwight, Illinois). THE hang-over state of chronic alcoholism and delirium tremens may be caused by a disturbance in acetylcholine metabolism.

The hepatic damage from alcohol may cause a depletion of cholinesterase, hence an excessive concentration of acetylcholine which, through its effects on the cerebral cortex might well be responsible for the disturbance of cerebral function in this ailment (as shown by abnormal fast and slow waves in EEG). (Barnes: Confinia Neurologica, 8, 73, 1948).

Esterase determinations were done according to a modified method of Alles and Hawes; 0.5 cc. of the blood

serum of the patient were mixed with 25 mg. acetylcholine in 20 cc. H_2O + 2 cc. buffer of pH 8, at 37°C.

The time was measured for the pH to drop from 8 to 7 (glass electrode). This esterase time is inversely related to the concentration of the esterase. No patients of over 60 years were considered since we confirmed Richter that the esterase in old age is low.

Forty-six alcoholic patients with mild or no hang-over had an esterase time value of 210 to 450 (mean 334 ± 7 seconds). Forty-seven alcoholic patients with *average* or *severe* hang-over symptoms, including 2 patients with delirium tremens, had an esterase time of 180 to 1,146 seconds (average 401 ± 14 seconds). The incidence of high esterase value (from low esterase content) was much higher in the severe alcoholics; there being no time values over 480 seconds (8 minutes) in the group of 47 patients with mild or no hang-over, but 10 cases in the group of 48 patients with severe or average hang-over, an incidence of 21%. It appears that the withdrawal (hang-over) symptoms of chronic alcoholism are caused by a poisoning with endogenous acetylcholine which accumulates because of an abnormally low esterase present in the blood serum (and probably also *true* esterase).

We have found (Anat. Record, 10, 739, 1915-16) that alcohol inhibits esterase of cat brain, when macerated cat brain is allowed to act on acetylcholine. Unpublished experiments demonstrate that cat brain esterase splitting mecholyl is also inhibited by alcohol. This shows that true tissue esterase is also poisoned by alcohol.

Of the numerous empirical treatments tried for alcohol poisoning and addiction, it would seem that those are most rational which build up the depleted cholinesterase. Liver extract or folic acid seems most suitable since, according to J. E. Davis (Fed. Proc., 8, 285, 1949), they produce cholinesterase *in vivo*, as well as *in vitro* from powdered liver. We found that administration of liver extract to alcoholics produces immediate recovery, working faster than the customary B_1, or other vitamins.

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BOOK REVIEWS AND NOTICES

NEURORADIOLOGY. By ALEXANDER OBLEY, M.D., Hon. Consulting Radiologist, West End Hospital for Nervous Diseases, London. Pp. 421; 572 ills. Springfield, Ill.: Charles C Thomas, 1949. Price, $11.50.

THIS book was prepared during the war years from material largely collected from the Hurstwood Park E. M. S. Neurological Hospital. The material is presented concisely and should serve a useful purpose. The entire cerebrospinal system is included. Most of the illustrations are reproduced as positives; many do not show the radiographic detail well. The pen and pencil sketches are very helpful.

The publisher has as usual maintained his high standard of excellence in the preparation of this book. The paper is very good and the type is easy to read. E. P.

ATLAS OF ORAL AND FACIAL LESIONS (AND COLOR FILM LIBRARY). By RALPH HOWARD BRODSKY, D.M.D., Consulting Oral Surgeon, Dept. of Hospitals, New York. Pp. 127; 100 figs. and 100 color lantern slides. Balt.: Williams & Wilkins, 1949. Price, $80.00.

THE author of this publication is well known and well qualified to write on this subject. The description text for each of the 100 Kodachrome reproductions is brief yet sufficiently complete. All of the common benign lesions and neoplasms are included in this atlas, as well as some of the less common conditions. General types of treatment are discussed.

More emphasis might have been given to a discussion of differential diagnosis. While the reviewer had an opportunity to examine only 3 of the separate Kodachrome reproductions, it was readily apparent that much of the original color values had been lost in the duplication.

Students and practitioners of Dentistry and Medicine should be familiar with this atlas.

L. B.

CURRENT THERAPY, 1949. Edited by HOWARD F. CONN, M.D., *et al.* Pp. 672. Phila.: W. B. Saunders, 1949. Price, $10.00.

THIS book, by 236 American Authorities, gives brief, specific methods for the treatment of practically all diseases that one is likely to meet in medical practice. Each article gives concise directions for the use of drugs and other therapeutic measures which the author employs in his own practice. In many conditions it describes the methods used by more than one authority; usually there is but little variation in the recommendations.

The pages are large, but the double column format makes reading easy. The book is divided into 14 sections, with the appropriate diseases arranged alphabetically in each section. There is a table of contents in the front of the volume, and a complete index of subjects and of authors in the back.

This is a book for which every doctor will find daily use. H. H.

BIOCHEMISTRY OF THE TEETH. By HENRY M. LEICESTER, Prof. of Biochemistry, Coll. of Phys. and Surg. of San Francisco. Pp. 306; 5 ills. St. Louis: C. V. Mosby, 1949. Price, $5.00.

THE book opens with considerations of tooth structure such as the fact, known for a century and a half, that teeth are composed of lime salts. Recently, the use of x-rays and the electron microscope has shown that the crystal lattice structure of enamel, dentin and bone resembles the naturally occurring mineral apatite. Nevertheless the physical properties of each of these structures differ.

A chapter on tooth formation including a discussion of the mechanism of calcification follows. Enamel differs from bone in being an epithelial derivative, and its organic matrix is probably a kerato-hyalin similar to that of keratins of hair and nails. Dentin has a collagenous ground substance which subsequently becomes calcified. Unlike bone, dentin is not normally subject to the physiologic withdrawal of calcium salts. The enzyme mechanisms involved in the process of calcification of all these structures are reviewed and discussed. The effect of vitamins and of hormones on developing teeth is reviewed. Finally the application of this biochemistry information to the problem of dental caries is considered.

This book has collected the references from many fields and presented findings with a critical discussion of technical methods and sources of discrepancies and disagreements.

P. B.

NEW BOOKS

Oncologia. Journal of Cancer Research: Prevention, Treatment and Sociological Aspect. Edited by E. BIANCHI and P. JUNG. Basel and New York: S. Karger, 1948. Price, 30 Swiss fr. a year.

This most recent of cancer journals appears quarterly as the official organ of the Swiss Nationalliga für Krebsbekämpfung. Manuscripts are accepted in German, English, French or Italian, with a Summary in all four languages. In the number sent for review (Vol. I, No. 3) the 6 titles cover an interesting range of subjects.

Symposium de Hematologia y Hemoterapia. Por el Dr. J. GUASH, *et al.* Pp. 522; illustrated. Barcelona, Spain: Miguel Servet, 1949. Price not given.

This first volume of projected Symposia on Hematology and Hemotherapy contains 7 articles on Penicillin in the treatment of the malignant neutropenias, simple and combined, Treatment of Kala-azar by splenectomy, Constitutional elliptocytosis, Leukemia and pregnancy, Blood picture in clinical allergy, Note on the distribution of the Rh factor in Spain, Therapeutics by the bone marrow way. A summary in English of each article will guide the English speaking reader through much tiring detail.

Biochemical Preparations, Vol. I. Edited by HERBERT E. CARTER, *et al.*, University of Illinois. Pp. 76. New York: John Wiley & Sons, 1949. Price, $2.50.

The first volume of this new series is very welcome to biochemists. Many compounds of biological interest have appeared in Organic Syntheses (as recorded on p. ix of this first volume). Nevertheless, there are many other compounds needed for biochemical research which must be made by the investigators themselves. Precise directions given in sufficient detail are of great assistance to those who must make a preparation for the first time. The present volume proposes to do this and has succeeded very well. It is hoped that Biochemical Preparations will be extended rapidly.
D. W.

Medical Latin. By CAROLYN LEWIS. Pp. 135. Francestown, N. H.: Marshall Jones, 1948. Price, $2.00.

An Outline of Psychoanalysis. By SIGMUND FREUD. Translated by JAMES STRACHEY. Pp. 127. New York: W. W. Norton, 1949. Price, $2.00.

Child Health Services and Pediatric Education. Report of the COMMITTEE FOR THE STUDY OF CHILD HEALTH SERVICES, THE AMERICAN ACADEMY OF PEDIATRICS. Pp. 270. New York: Commonwealth Fund, 1949. Price, $3.50.

"A nation-wide survey, the first that has ever been undertaken, of all the services and facilities currently available for the medical care and health supervision of infants and children throughout the country . . . and an analysis of present-day pediatric education."

Mayo Clinic Diet Manual. By COMMITTEE ON DIETETICS OF THE MAYO CLINIC. Pp. 329. Phila.: W. B. Saunders, 1949. Price, $4.00.

THIS is one of the best diet manuals written for the physician and dietician. Complete dietary programs for various medical and surgical conditions are outlined. Vitamin, caloric, and mineral requirements and values are given and quantities are listed in household equivalents and metric weights. An excellent section on pediatric dietetics is included.
G. R.

Pancreopatías Agudas no Dramáticas. Vols. I and II. Por ALFONSO ABELLAN AYALA. Pp. 32, 67. Barcelona, Spain: Col. Española de Monograf. Méd., Edic. Byp. 1949. No price given.

Mr. President—How Is Your Health? By KARL C. WOLD, M.D. Pp. 214. St. Paul and Minneapolis: Bruce Publishing Co., 1948. Price, $3.00.

DESPITE all that has been written about the lives of our Presidents, this is apparently the first attempt to set down their medical histories—30 presidents from Washington to F.D.R. Especially for the earlier presidents, a great deal is necessarily conjectural—even Washington's much discussed last illness—but the author has showed the courage of his convictions in almost always offering a definite diagnosis. His Final Analysis offers some interesting factual light on the effects on health of the responsibilities of this high office.
E. K.

NEW EDITIONS

Practical Bacteriology, Hematology and Parasitology. By E. R. STITT, M.D., PAUL W. CLOUGH, M. D., and SARA E. BRANHAM, M. D. 10th ed. Pp. 991; 765 ills, many in color. Phila.: Blakiston, 1948. Price, $10.00.

NEITHER the clinical pathologist nor the laboratory technician needs any introduction to this old stand-by. The present edition is very well prepared with good coverage of all phases of routine work in the clinical laboratory. The illustrations are well chosen and easily understood.
A. R.

Introduction to Physiological and Pathological Chemistry. By L. EARLE ARNOW, PH.G., PH.D., M.D., Director of Research, Sharp & Dohme. 3d ed. Pp. 595; 144 ills. St. Louis: C. V. Mosby, 1949. Price, $4.00.

Clinical Case-Taking. By GEORGE R. HERRMANN, M.D., PH.D., Prof. of Medicine, Univ. of Texas. 4th ed. Pp. 240. St. Louis: C. V. Mosby, 1949. Price, $3.50.

Human Biochemistry. By ISRAEL S. KLEINER, PH.D. 2d ed. Pp. 649; 77 ills., 5 color plates. St. Louis: C. V. Mosby, 1948. Price, $7.00.

KLEINER'S Human Biochemistry has been enlarged by about 75 pages. Many of the errors of the first edition have been corrected. A new chapter on Chemical Structure in relation to Biological Phenomena has been added. The references to clinical conditions are to be commended.
D. W.